From DEPARTMENT OF MEDICAL EPIDEMIOLOGY AND BIOSTATISTICS
Karolinska Institutet, Stockholm, Sweden

PARENTAL CANCER AND CHILDREN'S WELL-BEING: UNDERSTANDING THE POTENTIAL ROLE OF PSYCHOLOGICAL STRESS

Ruoqing Chen

Stockholm 2017

Front cover illustration by Xiaopeng Zhou.
Published by Karolinska Institutet.
Printed by E-Print AB 2017

ISBN 978-91-7676-652-1

Institutionen för Medicinsk Epidemiologi och Biostatistik

Parental cancer and children's well-being: understanding the potential role of psychological stress

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Atrium, Nobels väg 12B

Fredagen den 28 april 2017, kl 09.00

av

Ruoqing Chen

Huvudhandledare:
Docent Fang Fang
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Bihandledare:
Professor Unnur Valdimarsdóttir
University of Iceland
Faculty of Medicine
Centre of Public Health Sciences

Docent Katja Fall
Örebro University
School of Medical Sciences
Clinical Epidemiology and Biostatistics

Professor Kamila Czene
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Fakultetsopponent:
Professor Corinna Bergelt
University Medical Center Hamburg-Eppendorf
Department of Medical Psychology

Betygsnämnd:
Docent Ulf Jonsson
Uppsala University
Department of Neuroscience, Child and Adolescent Psychiatry

Docent Michael Fored
Karolinska Institutet
Department of Medicine (Solna)

Docent Jianguang Ji
Lund University
Center for Primary Health Care Research

Stockholm 2017

To the children

ABSTRACT

Early life stress has a major influence on one's health through the life course. During childhood, early experience may not only affect the normal brain development, but also influence the susceptibility to mental and physical disorders. A cancer diagnosis in a parent may cause substantial distress in the children, who may have to confront and adapt to short- and long-term changes in their lives and subsequently experience a higher risk of physical and psychosocial problems. Therefore, the first aim of this thesis was to examine whether parental cancer is associated with physical and mental health problems in the affected children using data from the Swedish national registers. Further, to explore the potential mechanism determining the impact of stress on children' health, we focused on the brain development in childhood and investigated the association between stress biomarkers and brain morphology, using data from a Dutch population-based cohort.

In Study I, we assessed the association between parental cancer and risk of injury in a large representative sample of Swedish children. We found that parental cancer was associated with a higher risk of hospital contacts for injury, particularly during the first year after the cancer diagnosis and when the parent experienced a psychiatric illness after the cancer diagnosis. The risk increment reduced during the second and third years and became null afterwards.

Given the observed higher risk of adverse physical health in terms of injury, we further investigated the influence of parental cancer on adverse mental health in terms of psychiatric disorders among children. In Study II, we constructed a matched cohort, and separately examined the associations between parental cancer diagnosed during pregnancy or after birth and clinical diagnoses of psychiatric disorders or use of prescribed psychiatric medications. Paternal but not maternal cancer during pregnancy appeared to be associated with a higher risk of psychiatric disorders, primary among girls. Parental cancer after birth conferred a higher risk of clinical diagnoses of psychiatric disorders, particularly stress reaction and adjustment disorders. The affected children also experienced a higher risk of use of prescribed psychiatric medications, particularly anxiolytics. The latter associations were most pronounced for parental cancer with poor expected survival and for parental death after cancer diagnosis.

In Study III, we focused on other domains of mental and physical health affected by parental cancer. We examined the associations of parental cancer with intellectual performance, stress resilience, and physical fitness among boys that underwent the compulsory military conscription examination during early adulthood. We observed positive associations of parental cancer with low stress resilience and low physical fitness, with stronger associations noted for parental cancer with poor expected survival and for a loss of parent through death after cancer diagnosis. No overall association was observed between parental cancer and intellectual performance, but the parental cancer with poor expected survival or resulting in a death of the parent was associated with a higher risk of low intellectual performance.

The hypothalamic-pituitary-adrenal (HPA) axis is one of the most extensively studied stress systems. Detection of glucocorticoids in hair has emerged as an approach to measuring HPA activity retrospectively. In Study IV, we assessed the associations of hair cortisol and cortisone concentrations with brain morphology in a population-based sample of young children in Rotterdam, the Netherlands. The regions of interest analyses showed that hair cortisol and cortisone concentrations were positively associated with cortical surface area in the parietal lobe. However, an inverse association was found between hair cortisol or cortisone concentration and hippocampal volume in children with behavioral problems. The vertex-wise analyses with correction for multiple testing did, however, not show any association of hair cortisol or cortisone concentration with cortical thickness, cortical surface area or gyrification.

In conclusion, parental cancer, a potent early life stressful event, is associated with a higher risk of physical and mental health outcomes, including injuries, psychiatric disorders, low intellectual performance, low stress resilience, and low physical fitness. Although we did not find clear associations of hair cortisol and cortisone concentrations with brain morphology in typically developing children, children that are evidently exposed to psychological stress should be provided adequate support and care to prevent from stress-related health outcomes.

LIST OF SCIENTIFIC PAPERS

I. Chen R*, Regodón Wallin A*, Sjölander A, Valdimarsdóttir U, Ye W, Tiemeier H, Fall K, Almqvist C, Czene K, Fang F. Childhood injury after a parental cancer diagnosis. *Elife*. 2015 Oct 31;4. pii: e08500.
*These authors contributed equally to this work

II. Chen R, Regodón Wallin A, Norén Selinus E, Sjölander A, Fall K, Valdimarsdóttir U, Czene K, Fang F. Psychiatric disorders among children with parental cancer: a Swedish register-based matched cohort study. *(Submitted)*

III. Chen R, Fall K, Czene K, Kennedy B, Valdimarsdóttir U, Fang F. Is parental cancer associated with intellectual, psychological and physical performance in early adulthood? *(Submitted)*

IV. Chen R, Muetzel RL, El Marroun H, Noppe G, van Rossum EF, Jaddoe VW, Verhulst FC, White T, Fang F, Tiemeier H. No association between hair cortisol or cortisone and brain morphology in children. *Psychoneuroendocrinology*. 2016 Aug 24;74:101-110.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention deficit/ hyperactivity disorder
HPA	Hypothalamic-pituitary-adrenal
ICD	International Classification of Diseases
MGR	Multi-Generation Register
ATC	Anatomical Therapeutic Chemical
HR	Hazard ratio
CI	Confidence interval
OR	Odds ratio
RRR	Relative risk ratio
MRI	Magnetic resonance imaging
BMI	Body mass index

1 INTRODUCTION

Psychological stress occurs when one appraises an environmental demand as challenging or threatening to cope with (1). Stressful life events have been used as a measure to quantify psychological stress and demonstrated to have significant impact on one's mental and physical health. Children are particularly vulnerable because of their immaturity and lack of autonomy and capacity to cope with psychological stress on their own.

A cancer diagnosis in a parent is often thought to essentially guarantee adverse outcomes over the course of the disease in the family. Compared to the relative abundance of research on cancer patients and their partners (2-6), less attention was devoted to assess the impact of parental cancer on children's well-being. The current knowledge about the consequence of parental cancer consists primarily of increased risks of emotional or behavioral problems (7, 8). Only a few studies addressed somatic health outcomes among these children (9-13). Many studies used a cross-sectional design, had small sample sizes, or used narrative data or different questionnaires as the outcome measurements, leading to potential bias, low statistical power and contradicting results. So far there have only been several studies evaluating the consequence of parental cancer in Sweden (14-17). Their findings showed that children that experienced a parent with cancer (e.g., lung cancer and esophageal cancer) or loss of parent with cancer exhibited a higher risk of distress, insomnia, fatigue, and self-injury. However, the general, short- and long-term health outcomes among the children with parental cancer remain largely unknown.

This thesis takes advantage of different epidemiological study designs to enrich the understanding of the association between psychological stress and children's well-being, by investigating the consequences of parental cancer on the physical and mental health of children. To explore the potential mechanism of stress-induced changes in the developing brain, this thesis also analyzes the brain structure in relation to stress biomarker levels in hairs among young children.

2 BACKGROUND

2.1 PSYCHOLOGICAL STRESS AND CHILDREN'S HEALTH

In daily life, humans are often confronted with challenges and demands. When the adaption or coping is of great difficulty or cannot be achieved, psychological stress arises. One can experience psychological stress from daily hassles (e.g. academic demands, financial considerations, and relationship problem) to stressful life events (e.g., divorce or separation, loss of a family member, and serious illness).

Compared with adults, children are in a critical period of physical growth and neurological development. The stressful life events may therefore yield short- and long-term negative impact disturbing the normal development, and elevate the susceptibility to the development of mental and somatic disorders (18).

Previous research has provided evidence for the consequence of exposure to early stressful life events, including parental divorce, physical and sexual abuse, bereavement as well as life-threatening situations such as wars (19-24). These experiences have led to increased risks of cognitive (e.g., impaired academic achievement), psychosocial (e.g., low self-esteem and social competence), psychiatric (e.g., depression, anxiety, alcohol/drug abuse, suicide attempt), and physical problems (e.g., ulcers and headache/migraine). Living with a parent with serious illness, such as cancer, has become more likely to occur during childhood, potentially as the result of early diagnosis due to screening programs and the increased parental age at first childbirth. The cancer diagnosis may pose an extraordinary challenge because children are not only confronted with altered family life situation and parental supervision, but also the threat of losing a parent and being diagnosed with cancer themselves (8, 25). So far no much research has been done on the impact of parental cancer on children's short- and long-term well-being on a population level.

The adverse impact of stress can be experienced by human beings even before birth. It has been demonstrated that maternal exposure to stress during pregnancy has short- and long-term effects on the developmental outcome of the fetus/child (26). Compared to stress after birth, prenatal exposure to stress has been associated with impaired fetal development and pathological birth outcomes, which may further contribute to the susceptibility to neurodevelopmental and neuropsychiatric disorders later in life (27).

2.2 PARENTAL CANCER

2.2.1 Prevalence of parental cancer

Data about the number of children with parental cancer or number of cancer patients with children are limited on population levels. According to a national health survey between 2000

and 2007 in the United States, 14% of adult cancer patients lived with minor children (28). The authors noted that these numbers might be an underestimation of the true affected population as children that did not live in the same household as their parents had not been taken into account. In Norway, approximately 4% of children younger than 25 years of age have experienced a parental cancer diagnosis, corresponding to a population prevalence of 1.4% (29). In Finland, around 6.6% of children at the age of 0-21 years have a parent suffering from cancer (30). The prevalence of children affected by parental cancer in Sweden has not been reported. According to the Swedish National Board of Health and Welfare, the number of newly diagnosed cancer patients has increased from 28,000 in the year 1970 to 65,000 in the year 2015 (31). Approximately 20-27 % of these patients were diagnosed at the age of 25-59 years, potentially parenting minor children.

2.2.2 Medical and psychological aspects of parental cancer

2.2.2.1 Diagnosis and treatment of cancer

The period shortly after cancer diagnosis (a few months to one year or more) is highly hectic. Patients may have to undergo more diagnostic examinations and to be confronted with decision making about treatment and care. The treatment options vary by age, type and stage of cancer, as well as other medical conditions of the patients. They usually include but are not limited to surgery, chemotherapy, radiotherapy, hormone therapy, biological therapy, and targeted therapy (32). Previous research has shown that patients with dependent children preferred aggressive treatment over palliative care (33). Treatment with longer duration and complications may lead to increased demand and burden on the family (34).

2.2.2.2 Severity and prognosis of cancer

Cancer staging system, such as TNM staging system, provides information about the size, extent and metastasis of a cancer based on the diagnosis (35). It helps patients and doctors understand the severity and chances of survival. If the cancer is diagnosed at an early stage, it is more likely to be treated successfully, and generally the patient's chance of survival is higher. However, younger age at diagnosis of some cancers, e.g., breast cancer and prostate cancer, is likely related to a worse prognosis (36, 37). The 5-year relative survival rate of cancers refers to the percentage of patients alive five years after their cancer is diagnosed, divided by the percentage of the general population alive after five years. It is often used to compare the prognosis of different cancers. In Sweden, the 5-year relative survival rate for all cancers has increased dramatically, from 35% in men and 48% in women in the early 1970s, to over 70% for both sexes in 2010 (38).

2.2.2.3 Parental psychological conditions

Cancer patients often experience emotional distress and psychiatric problems. According to a recent Swedish study, cancer patients have an increased risk of mental disorders, including stress reaction and adjustment disorders, depression, anxiety, substance abuse, dissociative

(conversion) disorders and somatoform disorders, from one year prior to diagnosis until ten years after diagnosis (39). The conditions of patients with advanced cancer are even worse: 50% meet the diagnostic criteria for psychiatric disorders (40). Some studies showed that patients with cancers such as lung and pancreatic cancers were most distressed (41). Other findings indicated, however, that patients with cancers of relatively better survival were more likely to have mental disorders than patients of cancers with poor prognosis (42). Intense treatment such as higher doses of chemotherapy has also been related to high distress (43). A poor psychological adaptation may not only affect the survival for the cancer patient, but also have a strong negative influence on the child's psychological well-being (44, 45).

2.2.3 Previous research – Having a parent with cancer

2.2.3.1 Prenatal exposure to parental cancer

Maternal cancer diagnosed during pregnancy has been associated with a higher risk of adverse birth outcome such as being born preterm and small for gestational age, and death due to perinatal and congenital conditions (46, 47). One recent multicenter study indicated that prenatal exposure to maternal cancer did not lead to cognitive, cardiac, or general health problems among children at the age of 3 years (48). These findings did not vary by cancer treatment status of mothers. Research about the prenatal exposure to paternal cancer is largely lacking. Children born to a father who were cancer survivors were more likely to have congenital abnormalities than those of fathers without history of cancer (49).

2.2.3.2 Postnatal exposure to parental cancer

Most studies have been focused on the emotional and behavioral functioning of the children who had a parental cancer. Compared with other children, children who had a parent with cancer experienced various emotions, such as guilt, sorrow, shyness, worry, anger, and fear of losing the parent (9, 11, 25). Children may not easily express their feelings, but manifest themselves by physical and emotional complaints, such as headache, sleeping difficulties, loss of appetite, withdrawal or aggression (12, 50-52). High risks of mental health problems have consistently been reported among the affected children, who were assessed using interviews, questionnaires and clinical diagnoses in qualitative and quantitative studies (53-56). School concentration and performance was also compromised in children of parents with cancer (11, 50, 57).

Parent and family-related characteristics have been strongly associated with children's psychosocial adjustment. Parental mental conditions contributed greatly to the vulnerability to psychosocial problems in children (58). Single parenthood has been associated with lower self-worth and social acceptance, and lower health-related quality of life in children with parental cancer (59, 60). Heathy family functioning such as increased family cohesion and open communication, on the contrary, has been associated with less stress-related symptoms, less internalizing and externalizing problems, and higher health-related quality of life in adolescents with parental cancer (44, 57, 61, 62).

2.3 CHILDREN'S HEALTH

According to the World Health Organization, well-being entails one's experience of their life and a comparison of life circumstances with social norms and values (63). Both physical and mental health are important contributors to well-being.

2.3.1 Physical health

Injury is the most common cause of health care for children. It accounts for approximately one million deaths of children per year in the world (64). It has been well documented that occurrence of childhood injury is strongly determined by sociodemographic, behavioral and psychosocial factors in the family (65). Life events such as parental unemployment, frequent changes of residence, and parental divorce or separation have been associated with a higher risk of childhood injury. Moreover, parental illness such as migraine, back pain, and depression has also been reported to correlate with a higher likelihood of injury in children (66). The association between parental cancer and childhood injury has not yet been specifically investigated.

Injury may reflect an acute impact of environmental changes. Physical fitness, on the other hand, entails the development of cardiorespiratory endurance, muscular endurance and strength, body composition and flexibility (67). Low physical fitness has been associated with a higher risk of cardiovascular disease, metabolic disease, as well as premature mortality (68-70). To evaluate the impact of parental cancer on children's physical health in the short and long run, we studied both injury and physical fitness in this thesis.

2.3.2 Mental health

Mental health problems are one of the main categories of disorders faced in children's health services. Psychiatric disorders refer to a wide variety of mental health conditions with ongoing symptoms affecting one's mood, behavior and functioning. In Sweden, the most common psychiatric disorders diagnosed in children include mood disorders, anxiety, attention deficit/ hyperactivity disorder (ADHD), and autism spectrum disorder (71). Previous research has indicated that genes and dysfunction of central neural network contributes to certain types of psychiatric disorders (72, 73). Exposure to environmental stressors both before and after birth has also substantial impact on the development of psychiatric disorders (74).

There has been strong support for the notion that early life stress is a risk factor for psychiatric conditions (75), not much research has however assessed how it affects the ability of adaptation and recovery from adversities and related psychological stress. Stress resilience refers to the capacity for adaptively overcoming challenging or threatening circumstances and maintaining normal psychological functioning (76). The development of stress resilience may be restricted by the damaging effects on neural structures from early life stress (77).

A growing number of literatures have examined the associations between mental health problems and brain development in relation to psychological stress (78, 79). For example, early adversities, such as family instability and abuse, may be associated with variation in gray matter volumes directly or mediated by internalizing problems (78). Childhood traumas have also been associated with both smaller hippocampal volume (80, 81) and lower intellectual capacity in middle adulthood (82). To gain a comprehensive understanding of children's mental health affected by psychological stress, we examined psychiatric disorders, stress resilience, intellectual performance as well as brain morphology among children in this thesis.

2.4 POTENTIAL MECHANISMS UNDERLYING THE IMPACT OF PSYCHOLOGICAL STRESS

2.4.1 Stress system

When the brain detects a challenge or threat, the physiological response involves an immediate stimulation of muscles and organs and a subsequent response involving neuroendocrine, metabolic, immune and autonomic systems (83).

The main stress systems and factors involved in stress response include the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, metabolic hormones, and inflammatory cytokines (83). HPA axis has been most extensively studied. Neurons in the hypothalamus release corticotropin-releasing hormone and arginine vasopressin, which stimulate the production of adrenocorticotropic hormone from the pituitary gland, and subsequently lead to the secretion of glucocorticoids from the adrenal cortex. The HPA axis activity is partially determined by the regulation of adrenocorticotropic hormone and corticotropin-releasing hormone through glucocorticoids' binding to corticosteroid receptors, and controlled by feedback loops that tend to maintain a homeostatic state of the organism (84).

2.4.2 HPA axis activity and brain development

Glucocorticoids are commonly used as stress biomarkers as they are the final effector and key regulator of the HPA axis (85). In humans, cortisol is the most common glucocorticoids. Cortisol can be converted by the 11β-hydroxysteroid dehydrogenase type 2 enzyme into inactive metabolite cortisone, which represents another useful stress biomarker (86). The assessment of glucocorticoids in hairs has been used to retrospectively evaluate the cumulative glucocorticoids production over the past several months, and provides good opportunity for exploring the association between prolonged HPA axis functioning and brain development (87, 88).

Glucocorticoids play a key role in maintaining normal brain function and maturation (89). They initiate terminal maturation, remodel axons and dendrites, as well as affect programmed

cell death (83). Excessive glucocorticoid exposure may however exert adverse effects on the brain structure and function, including altered synaptic terminal structure, reduced dendritic branching, inhibition of neuronal regeneration, disrupted cellular metabolism, and increased vulnerability of hippocampal neurons to metabolic insults (90). In humans, cortisol reactivity and variation of the cortisol circadian rhythm have been associated with memory, language comprehension, as well as emotional and behavioral problems in children (91-94). Given the late introduction of brain imaging in pediatric research settings, few studies have so far investigated the association of HPA axis activity with brain structure or function in children (95, 96).

3 AIMS

This thesis aims to contribute to the understanding of the association between psychological stress and health in children, by examining 1) the impact of parental cancer on physical and mental health among the affected children and 2) the association between long-term HPA axis activity and brain morphology among typically developing young children.

Specifically, it aims:

- To examine the association between parental cancer and hospital contacts for injury among children (Study I);
- To examine the association between parental cancer diagnosed during pregnancy or after birth and psychiatric disorders among children (Study II);
- To examine the association of parental cancer with intellectual performance, stress resilience and physical fitness among young adult men (Study III);
- To examine the association between hair cortisol or cortisone concentration and brain morphology among young children (Study IV).

4 METHODS

4.1 PARENTAL CANCER AND CHILDREN'S WELL-BEING (STUDIES I, II & III)

4.1.1 Data sources

All data used in Studies I, II and III were obtained from the Swedish national registers. The unique ten-digit personal identity number assigned to each Swedish resident enables individual data linkage across all registers (97).

4.1.1.1 Swedish Multi-Generation Register

The Swedish Multi-Generation Register (MGR) consists of data on all residents in Sweden who were born in 1932 or later and alive in 1961. These individuals are referred to as index persons. Familial linkage is available between the index persons and their parents (biological and adoptive if there is any). The coverage was 100% in the biological maternal information and 98% in the biological paternal information for those born from 1961 onward (98). Information used in this thesis included: date of birth, sex and country of birth of index persons (i.e., children in the present studies), and date of birth of their parents. This register was also used to identify siblings of the index persons.

4.1.1.2 Swedish Cancer Register

The Swedish Cancer Register was launched in 1958 and has been mandatory for all physicians (as well as pathologists and cytologists if involved during diagnosis) to report new cases of cancer. The reporting to the Cancer Register approaches almost 100% of all newly diagnosed cancer cases in Sweden (99). Information used in this thesis included: clinical diagnosis indicated by the 7th Swedish revision of the International Classification of Diseases (ICD) codes (140-205) and date of diagnosis (100).

4.1.1.3 Patient register

The Patient Register was founded in 1964 and has since collected individual-based information on inpatient care (101). It has nationwide coverage of all hospital discharges from 1987 onward. Since 2001, it also includes information of hospital-based outpatient visits to specialist care conducted by doctors with around 80% coverage in Sweden. Information used in this thesis included date of admission, date of discharge, primary diagnosis, secondary diagnoses, external causes of morbidity and mortality. Diagnoses and external causes were all indicated by the Swedish revisions of the ICD.

4.1.1.4 Prescribed Drug Register

The Prescribed Drug Register was established in July 2005. It contains information of all dispensed prescriptions at pharmacies in Sweden (102). All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) system. Information used in this thesis included ATC codes for dispensed items and date of dispensing.

4.1.1.5 Military Service Conscription Register

Until the year 2010, military conscription was mandatory for all Swedish young men except those with known handicaps, severe mental and physical health problems, or being incarcerated (103). Every healthy young man had to undergo a two-day examination at the age of 18 years, or in some cases at a later occasion. The Conscription Register provides detailed information on intellectual, psychological, physical and medical assessments on all conscripts during the examination (104). Information used in this thesis included date of examination, scores of intellectual performance, stress resilience and physical fitness.

4.1.1.6 Medical Birth Register

The Medical Birth Register was initiated in 1973 and aims to compile information on prenatal, delivery and neonatal factors from medical records (105). It has a 98-99% coverage of all births in Sweden over the years. Information used in this thesis included birth weight, and gestational age and mode of delivery at birth of the child, and maternal smoking during pregnancy.

4.1.1.7 Register of Education

The Register of Education was established in 1985. It collects information on the highest level of education for all individuals living in Sweden at the age of 16-74 years (106). The highest obtained education is classified into eight levels: 0) no education, 1) compulsory school less than 9 years, 2) compulsory school for 9 years, 3) upper secondary school for 2 years or less, 4) upper secondary school for 3 years, 5) tertiary education less than 3 years, 6) tertiary education for 3 years or more, and 7) postgraduate education. In this thesis, we created categories of primary school or lower (0-2), secondary education (3-4), tertiary education (5-6), and postgraduate education (7).

4.1.1.8 Other Registers

Information on the date of emigration was collected from the Migration Register. The Cause of Death Register includes information on all deceased individuals that were registered in Sweden at the time of death. Information on the date of death was used in this thesis. Information on the socio-economic statuses of the parents were obtained from the Swedish Population and Housing Census in 1980 and classified into four categories: 1) blue-collar, 2) white-collar, 3) self-employed including farmers, and 4) others (107).

4.1.2 Ascertainment of exposure and outcome

4.1.2.1 Parental cancer

The exposure was defined as a parental cancer diagnosed during pregnancy (i.e., prenatal exposure; Study II) or after birth (i.e., postnatal exposure; Studies I, II and III).

Both parents of the children were linked to the Cancer Register, and the date of first cancer diagnosis, if any, was identified. In case that both parents had a cancer diagnosis, the first one

was studied. As the aim was to evaluate the impact of newly diagnosed parental cancer, children whose parents were diagnosed with cancer before the pregnancy (Study II) or their birth (Study I and Study III) were excluded. In addition to the overall impact, we were particularly interested to know whether the impact: 1) varies by the sex of parent with cancer, 2) varies in time since cancer diagnosis (the immediate response to the "crisis"), 3) varies across different expected survival for parental cancer (disease severity or prognosis based on diagnosis) (Table 1), and 4) differed before and after the death of the parent with cancer (the ultimate outcome of parental cancer).

Table 1. Expected 5-year survival classified by the predicted 5-year relative survival of each cancer type, according to summarized data from the National Board of Health and Welfare and Swedish Cancer Society (38, 108)

Expected 5-year survival	Predicted 5-year relative survival rate	Cancer types
Poor	< 20%	esophagus, liver, gall bladder, biliary tract, pancreas, lung and stomach
Moderate	20–80%	oral cavity, pharynx, small intestine, colon, rectum, other digestive organs, nose, nasal cavities, middle ear and accessory sinuses, larynx, mediastinum and other thoracic organs, cervix uteri, ovary and other female genital organs, prostate and other male genital organs, kidney, bladder and other urinary organs, eye, brain, bone, connective tissue, Non-Hodgkin's lymphoma, multiple myeloma, leukemia, and unspecified sites
Good	≥ 80%	lip, breast, corpus uteri, testis, skin, thyroid and other endocrine glands, and Hodgkin's lymphoma

4.1.2.2 Injury

In Study I, the primary outcome was defined as a hospital contact for injury among children. It was determined by either a hospital admission or an outpatient visit with a diagnosis of injury through linkage to the Patient Register. As we were mainly interested in injuries not related to medical care, only children with both a main diagnosis of injury (ICD 10: S00-T98 except T80-T88, T98.3) and an external cause for that injury (ICD 10: V01-Y98 except Y40-Y84, Y88) were included. Injuries resulting from complications of medical and surgical care were excluded. Injuries were further classified by nature, body region (based on the main diagnosis), and by manner or intent, mechanism of injury and place of injury occurrence (based on the external cause) (Table 2) (109).

We were interested to know whether parental cancer was associated with: 1) any hospital contact for injury, and 2) recurrent hospital contacts for injury. For the second question, we focused on children that had visited hospital due to injury more than once, and took into account all hospital contacts during follow-up (see section 4.1.3.1) in the analysis.

Table 2. Characteristics of injuries classified by the ICD 10

Characteristics of injuries	ICD-10
Manner or intent	
Unintentional	V01–X59, Y85–Y86
Intentional self-harm	X60–X84, Y87.0
Assault	X85–Y09, Y87.1
Undetermined or other	Y10–Y36, Y87.2, Y89–Y98
Nature	
Fracture	S02, S12, S22, S32, S42, S52, S62, S72, S82, S92, T02, T08, T10, T12, T14.2, T90.2, T91(.1,.2), T92(.1,.2), T93(.1,.2)
Contusion or superficial injury	S00, S05(.0,.1), S10, S20, S30, S40, S50, S60, S70, S80, S90, T00, T09.0, T11.0, T13.0, T14.0, T90.0
Open wound	S01, S05(.2–.7), S08.0, S09.2, S11, S21, S31, S41, S51, S61, S71, S81, S91, T01, T09.1, T11.1, T13.1, T14.1, T90.1, T92.0, T93.0
Internal organ injury	S06, S14(.0–.2), S24(.0,.1), S26.0, S27(.0–.6, .8–.9), S34(.0,.1,.3), S36, S37, S39(.6,.7), T06.5, T09.3, T90.5, T91(.3–.5)
Effect of foreign body entering orifice	T15–T19, T98.0
Dislocation	S03(.0–.3), S13(.0–.3), S23(.0–.2), S33(.0–.4), S43(.0–.3), S53(.0,.1), S63(.0–.2), S73.0, S83(.0,.1), S93(.0,.1, .3)
Other	S03(.4,.5), S04, S05(.8, .9), S07, S08(.1–.9), S09(.0,.1,.7,.8,.9), S13(.4–.6), S14(.3–.6), S15–S18, S19, S23(.3–.5), S24(.2–.6), S25, S26(.8, .9), S27.7, S28, S29, S33(.5–.7), S34(.2, .4,–.8), S35, S38, S39(.0,.8,.9), S43(.4–.7), S44–S49, S53(.2–.4), S54–S59, S63(.3–.7), S64–S69, S73.1, S74–S79, S83(.2–.6), S83.7, S84–S89, S93(.2, .4–.6), S94–S99, T03–T05, T06(.0–.4,.8), T07, T09(.2, .4–.9), T11(.2–.9), T13(.2–.9), T14(.3,–.9), T20–T79, T90(.3,.4, .8,.9), T91(0., .8, .9), T92(.3,–.9), T93(.3,–.9), T94–T97, T98(.1,.2)
Body region	
Upper extremity	S40–S69, T00.2, T01.2, T02(.2,.4), T03.2, T04.2, T05(.0,.1,.2), T10, T11, T22, T23, T33 (.4,.5), T35.4, T92, T95.2
Head and neck	S00–S11, S12(.8–.9), S13(.2,.3,.5,.6), S14(.3–.6), S15(.0, .2–.9), S16, S17, S18, S19, T00.0, T01.0, T02.0, T03.0, T04.0, T15–T16, T17(.0–.4), T18.0, T20, T26,T27(.0,.4), T28(.0,.5), T33(.0,.1), T34(.0,.1), T35.2, T90, T95.0
Lower extremity	S70–S99, T00.3, T01.3, T02(.3, .5), T03.3, T04.3, T05(.3,.4,.5), T12, T13, T24, T25, T33(.6–.8), T34(.6–.8),T35.5, T93, T95.3
Trunk	S12(.0–.7), S13(.0,.1,.4), S14(.0–.2), S15.1, S20–S39, T00.1, T01.1, T02.1, T03.1, T04.1, T06.0, T06.5, T08, T09, T17(.5–.9), T18(.2–.4), T18(.1,.5,.8,.9), T19, T21, T27(.2,.3,.6,.7), T28(.1–.3,.6–.8), T33(.2–.3), T34(.2–.3),T35.3, T91(.1–.5), T95.1

Characteristics of injuries	ICD-10
Other	T00(.6,.8,.9), T01(.6,.8,.9), T02(.6,.7,.8,.9), T03(.4,.8,.9), T04(.4,.7,.8,.9), T05(.6,.8,.9), T06(.1–.4,.8), T07, T14, T27(.1, .5), T28(.4,.9), T29, T30–T32, T33.9, T34.9, T35(.0,.1,.6,.7), T36–T79, T91(.0,.8,.9), T94, T95(.4,.8,.9), T96, T97, T98(.0–.2)
Mechanism	
Fall	W00–W19, X80, Y01, Y30
Struck by or against	W20–W22, W50–W52, X79, Y00, Y04, Y29, Y35.3
Transport	V01–V99, X82, Y03, Y32, Y36.1
Nature, animal or plant	W53–W64, X20–X39
Cut or pierce	W25–W29, W45, X78, X99, Y28, Y35.4
Poisoning	X40–X49, X60–X69, X85–X90, Y10– Y19, Y35.2
Other	W23, W24, W30–W44, W46, W49, W65–W99, X00–X19, X50–X59, X70–X77, X81, X83, X84, X91–X98, Y02, Y05–Y09, Y20–Y27, Y31,Y33, Y34,Y35(.0,.1,.5,.6,.7), Y36(.0,.2–.9), Y85–Y87, Y89–Y98
Place of occurrence	
Residential area	W00(.0, .1)–Y05(.0, .1),Y08(.0, .1) –Y34(.0, .1)
Transportation area	V01–V99, W00.4–Y05.4,Y08.4–Y34.4
Sports and athletics area	W00.3–Y05.3,Y08.4–Y34.3
School, other institution or public administrative area	W00.2–Y05.2,Y08.2–Y34.2
Other	W00(.5,–.9) –Y05(.5,–.9), Y06, Y07, Y08(.5,–.9)–Y34(.5,–.9), Y35–Y36, Y85–Y87, Y89, Y90–Y98

4.1.2.3 Psychiatric disorder

4.1.2.3.1 Clinical diagnosis of psychiatric disorder

In Study II, the first outcome of interest was a clinical diagnosis of psychiatric disorder. Through the Patient Register, we identified children that had a main or secondary diagnosis of psychiatric disorder (ICD-10: F00-F99) from a hospital admission or an outpatient visit during follow up (see section 4.1.3.2). We were particularly interested to know whether parental cancer had an impact on specific types of psychiatric disorders, including: 1) affective disorders (F30-F39), 2) anxiety disorders [F40-F42, F44-F45, F48, F93(.0, .1, .2, .8)], 3) stress reaction and adjustment disorders (F43), 4) substance use disorders (F10-F19), 5) eating disorder (F50), 6) autism spectrum disorder (F84), and 7) ADHD (F90).

4.1.2.3.2 Prescribed psychiatric medication

To further evaluate the impact of parental cancer on the children's psychiatric conditions, we encompassed the prescribed psychiatric medication as a second outcome of interest in Study II. We extracted information from the Prescribed Drug Register on several psychiatric

medications that have commonly been prescribed for children, including antidepressants (ATC: N06A), anxiolytics (ATC: N05B), and hypnotics and sedatives (ATC: N05C) (110).

4.1.2.4 Intellectual performance

Intellectual performance was assessed in the conscripts using three different test versions during the study period (see section 4.1.3.3) (111). The overall test contents were similar, which consisted of four domains investigating inductive, verbal, spatial and technical abilities (111, 112). A global intelligence score was derived through summing scores from all domains, and standardized to present a Gaussian distribution with values between 1 and 9 (i.e., Stanine scale). A higher value indicated better intellectual performance. To evaluate whether parental cancer is associated with poor intellectual performance in Study III, we grouped the scores into three levels: low (1−3), moderate (4−6) and high (7−9) (113).

4.1.2.5 Stress resilience

The assessment of stress resilience was performed to evaluate the conscript's ability to cope with psychological stress during military service and ultimate armed combat (114, 115). Overall, capability to cope with loss of personal freedom and emotional stability were requirements for a high score, in addition to willingness to assume responsibility, high independence, persistence, ability to take initiative, and social capacity to contribute to group cohesion. In contrast, tendencies towards antisocial or aggressive behaviors, and difficulties in accepting authority or adjustment issues were considered negative factors. Four psychological dimensions including mental energy, emotional control, social maturity and active/passive interests were rated and combined to produce a summarized score of stress resilience on a Stanine scale. To assess whether parental cancer was associated with low stress resilience in Study III, we condensed the scores into low (1−3), moderate (4−6) and high (7−9) where a higher value indicated better functioning (116).

4.1.2.6 Physical fitness

Physical fitness was assessed by the maximal work test developed by Torn (117). During the test, the conscript was required to work on a bicycle ergometer, with gradually increasing resistance until volitional exhaustion (118, 119). The result of the test was expressed as the maximal work rate that the conscript could sustain for six minutes ($W_{max\ 6min}$). This was estimated by entering the values of the arbitrary work rate (kpm/minute) and the work time (minute) in the equation (119):

$$LogW_{max\ 6\ min} = \frac{LogT - Log6}{4.959} + LogN$$

The $W_{max\ 6min}$ were transformed into scores from 0 to 9, with a higher value indicating greater physical fitness. To assess whether parental cancer was associated with low physical fitness in Study III, we grouped the scores into low (0-4), moderate (5-7), and high (8-9).

4.1.3 Study designs

4.1.3.1 Study I

Study I was a register-based cohort study including 1,964,627 children born in Sweden during 1983–2002. The flow of inclusion and exclusion process is illustrated in Figure 1.

As data on outpatient visit were available from 2001 in the Patient Register, all children were followed from January 1, 2001 or date of birth, whichever came later. Person-time experienced by the children with parental cancer was counted first into the unexposed period and after the date of parental cancer diagnosis into the exposed period. If one's parent was diagnosed with cancer before January 1, 2001, all person-time was counted into the exposed period. Person-time experienced by the children without such exposure was all counted into the unexposed period (Figure 2). In the primary analysis, the follow-up was censored for both exposed and unexposed periods at the earliest of: 1) date of first hospital contact for injury, 2) date of emigration, 3) date of death, 4) date of 18th birthday, and 5) December 31, 2010 (Figure 2-A). In the secondary analysis, we extended the follow-up among children who were censored due to injury in the primary analysis, from the end of the wash-out period (we assumed that diagnoses of injuries occurring within a 7-day wash-out period were likely referring to a same diagnosis) to the following injuries (Figure 2-B).

4.1.3.2 Study II

Study II was a register-based matched cohort study, consisting of 1,047 children with and 10,470 without prenatal exposure to parental cancer, and 100,292 children with and 1,002,920 without postnatal exposure to parental cancer, during 1983–2010. The flow of inclusion and exclusion process of the matched cohort is illustrated in Figure 3. Note that the entry date was date of the start of follow-up for both the exposed and the matched unexposed children. It was either the date of parental cancer diagnosis (i.e., index date) or January 1, 2001, whichever came later. Both the exposed and unexposed children were followed from the entry date until the diagnosis of psychiatric disorder, death, emigration or December 31, 2010, whichever occurred first. The unexposed children were also censored when they became exposed.

In the analysis of prescribed psychiatric medications, children that were censored before July 1, 2005 due to death, emigration or becoming exposed were excluded, leaving 1,103,410 in the analysis. These children were followed for any psychiatric prescription until the date of parental cancer diagnosis (only applied to unexposed children), death, emigration or December 31, 2010, whichever occurred first.

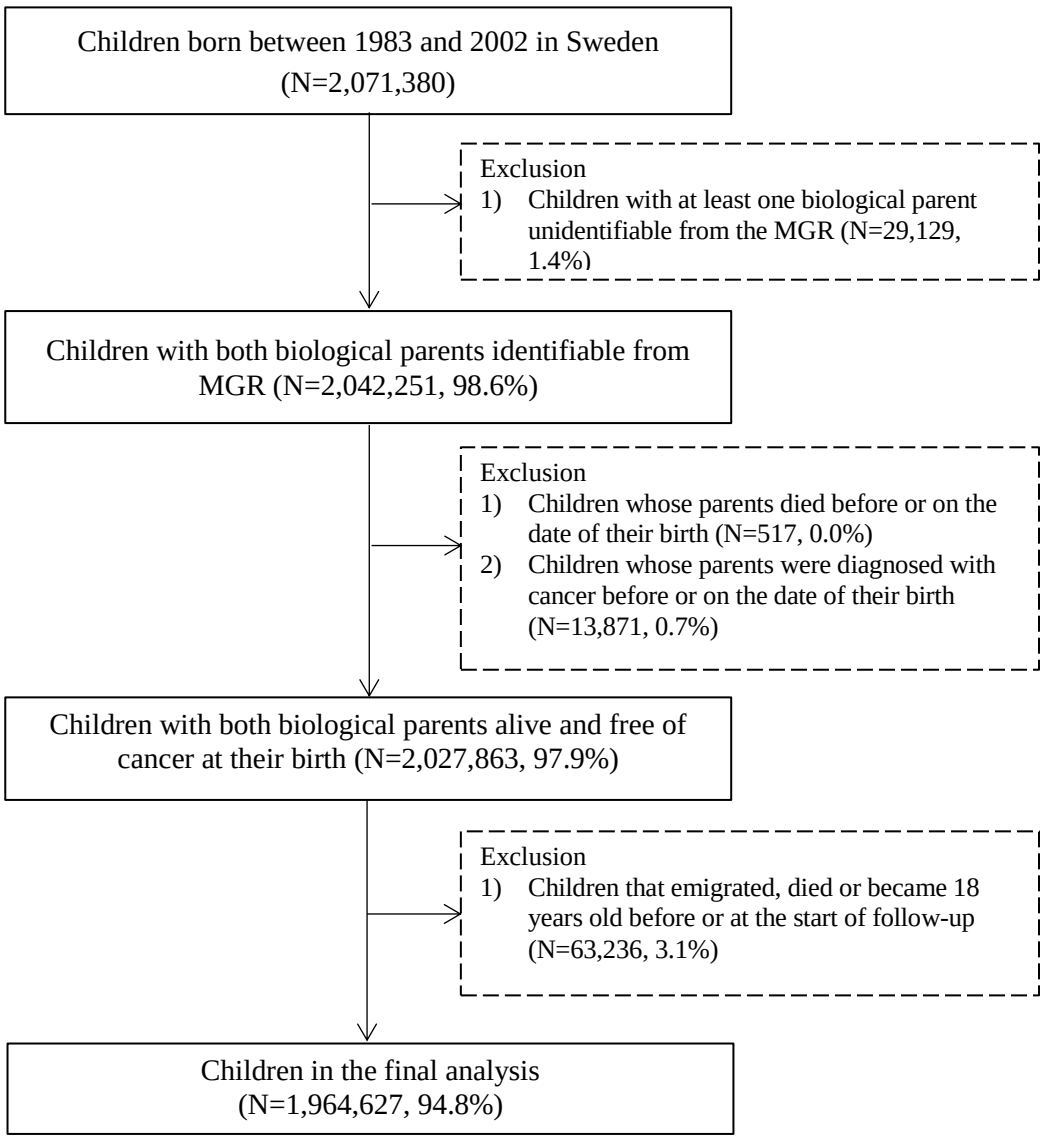


Figure 1. Flow chart of inclusion and exclusion of study participants in Study I

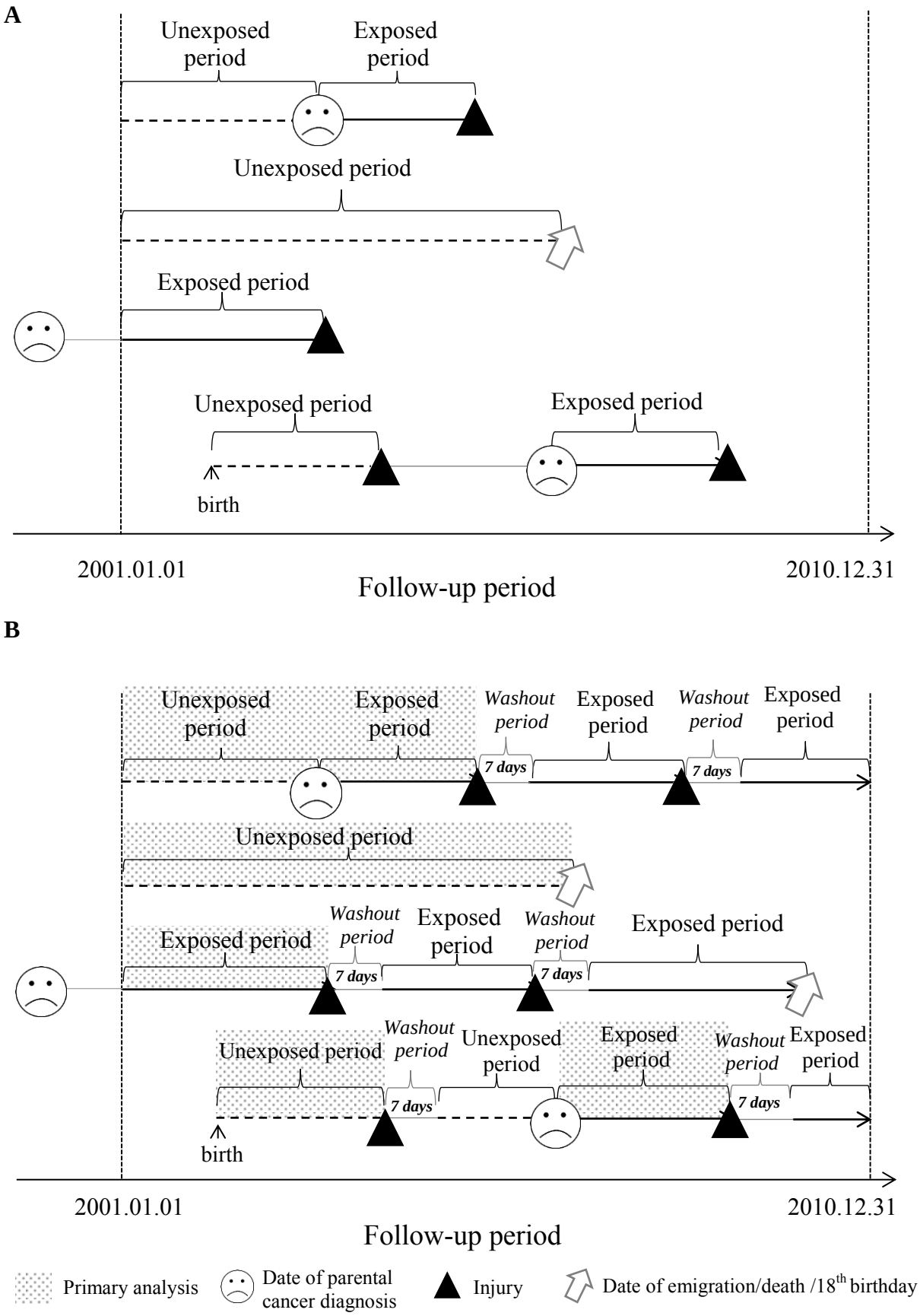


Figure 2. Follow-up in Study I (A: primary analysis. B: secondary analysis)

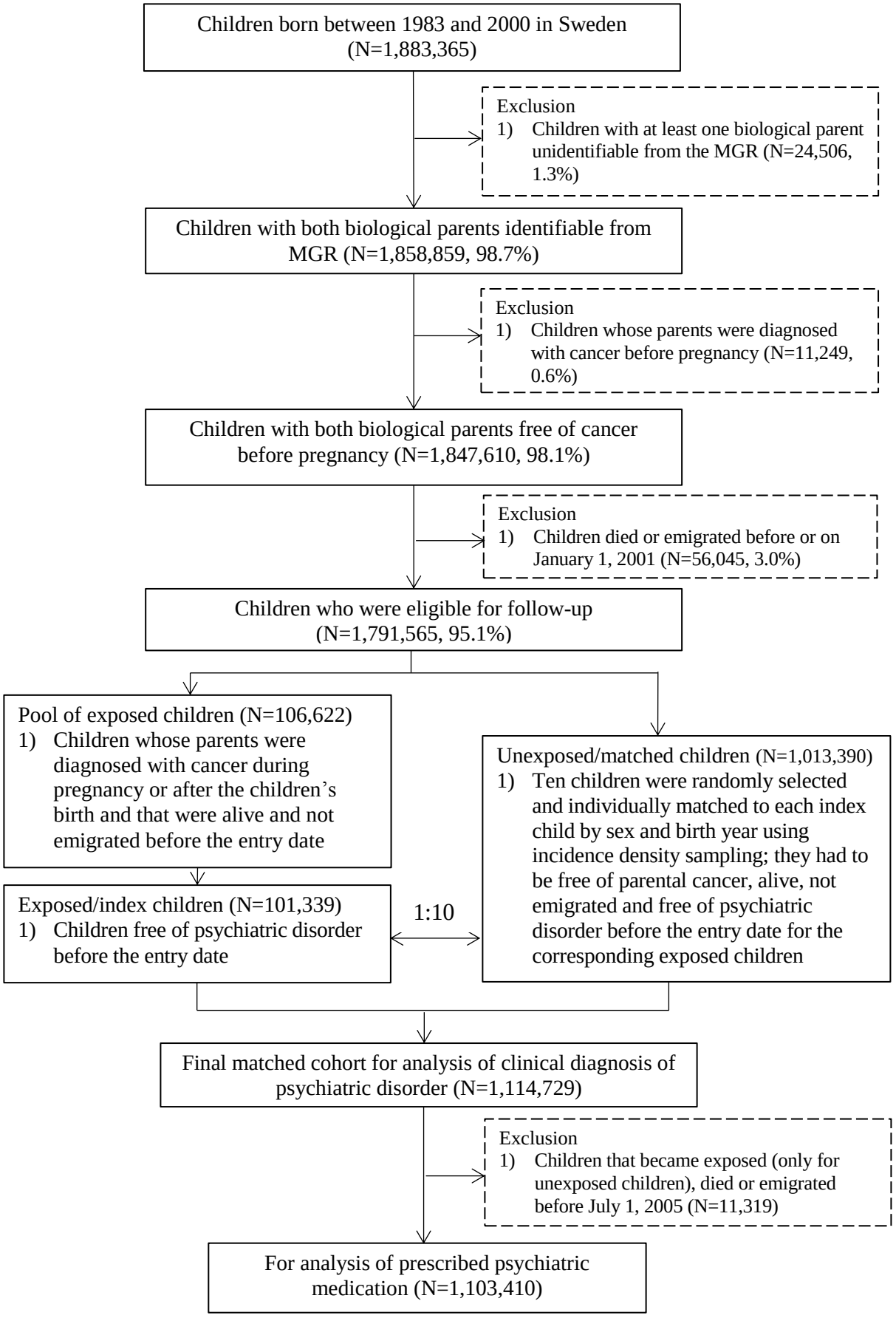


Figure 3. Flow chart of inclusion and exclusion of study participants in Study II

4.1.3.3 Study III

In Study III, we included 465,249 boys born in Sweden between 1973 and 1983 that underwent the conscription examination including assessments for intellectual performance, stress resilience and physical fitness. Figure 4 shows the flow of inclusion and exclusion process of the study participants.

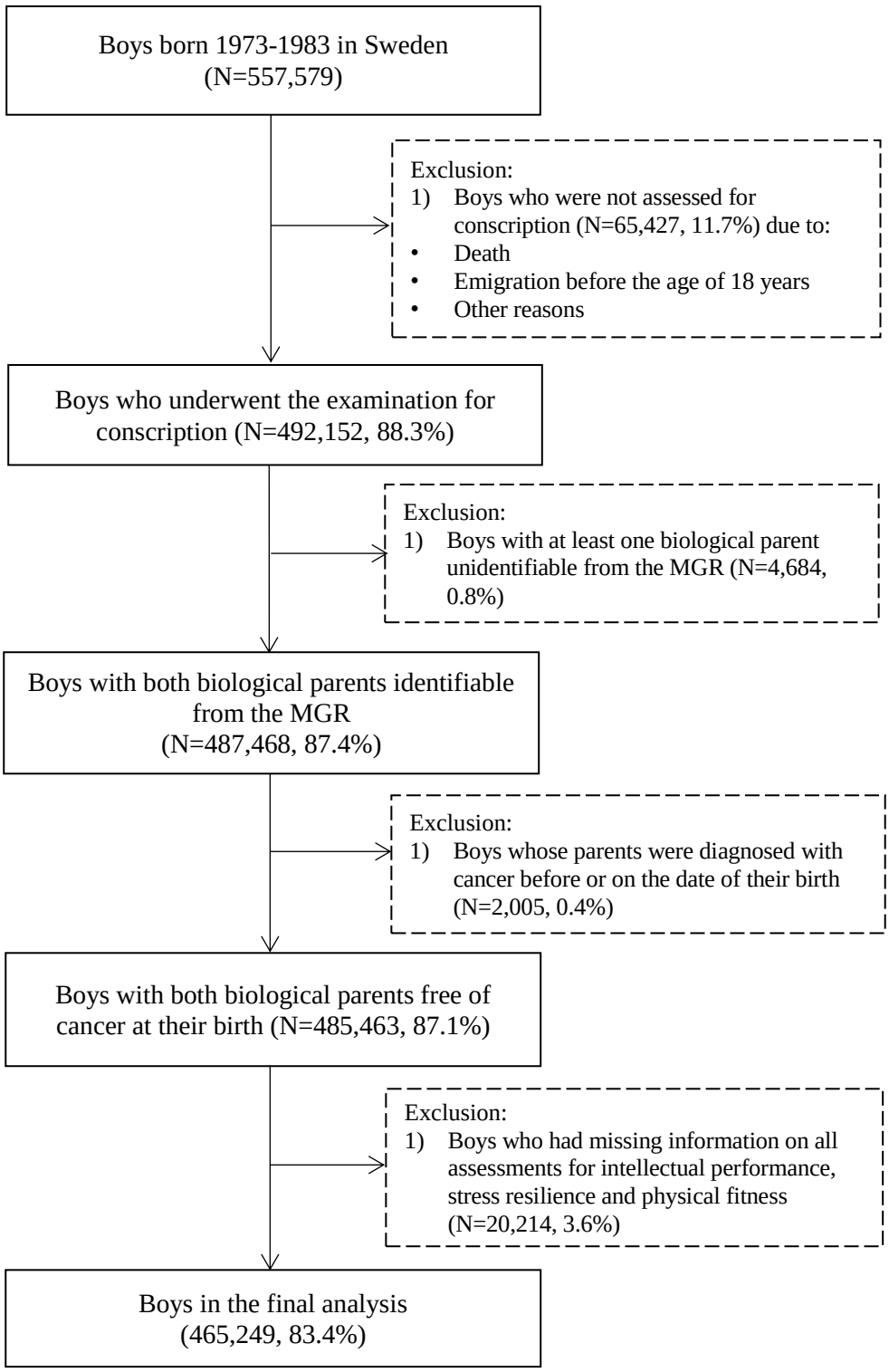


Figure 4. Flow chart of inclusion and exclusion of study participants in Study III

4.1.4 Statistical analysis

Pearson's χ^2 test was used to compare characteristics of the children and their parents between the exposed and unexposed groups.

4.1.4.1 Cox Proportional Hazards Regression (Studies I and II)

Cox proportional hazards regression (hereinafter called the Cox model) is one of the most common regression techniques for survival analysis, which aims to analyze follow-up time from a starting point in time until the occurrence of an event of interest. We applied the Cox model in Studies I and II, where we estimated the hazard ratio (HR) with 95% confidence interval (CI) for the first hospital contact for injury or clinical diagnosis of psychiatric disorder associated with parental cancer. The models were adjusted for a number of covariates described below. We tested the proportional hazards assumption on the basis of Schoenfeld residuals, and no statistically significant violation was observed in either study (120).

To assess the risk of repeated injuries in Study I, the original Cox model was not appropriate as it models only time to the first event. We instead used a conditional Cox model (Prentice, Williams and Peterson – Total Time model) (121). This model analyzed multiple injuries by stratifying on injury order during the follow-up period, with the assumption that a child was not at risk for a subsequent injury until a prior injury had occurred.

4.1.4.2 Logistic Regression (Study II)

We used logistic regression to compare between children with and without parental cancer the risk of any use of prescribed psychiatric medication and the risk of any use of antidepressants, anxiolytics, or hypnotics and sedatives during follow-up. Odds ratio (OR) with 95% CI was estimated with adjustment for several covariates (listed below) in the model.

4.1.4.3 Multinomial logistic regression (Study III)

Multinomial logistic regression is an extension of traditional logistic regression that models outcome variables of more than two categories. We estimated the relative risk ratio (RRR) with 95% CI for moderate or low level of intellectual performance, stress resilience or physical fitness versus high level (reference category) comparing between conscripts with and without parental cancer. We presented only results for low intellectual performance, low stress resilience and low physical fitness (see results for the moderate level of outcomes in the manuscript). A number of covariates were adjusted for in the analysis (see below).

To address potential confounding and effect modification, we included in analyses the following variables: sex, age or birth year, gestational age at birth, birth weight, mode of delivery, number of siblings of the children, maternal smoking during pregnancy, parental ages at child's birth, and educational level and socio-economic status of the parents. A parental psychiatric disease before the index date was also included in Study II.

We performed Wald tests to compare the HRs, ORs or RRRs among different exposed subgroups categorized by: 1) time since cancer diagnosis, 2) sex of the parent with cancer, 3) expected 5-year survival for cancer, 4) parental death after cancer diagnosis, and 5) parental comorbid psychiatric disease after cancer diagnosis. The Wald tests were also performed to test the dose-response trend in the analysis of expected 5-year survival for cancer.

We used formal tests of interaction to examine the potential modifying effect of sex and age at follow-up of the child, and parental history of psychiatric disease on the studied associations.

Robust standard errors were applied in all models to account for the non-independence of data on children from the same family.

The data preparation was performed using SAS version 9.4, SAS institute Inc.. The statistical analyses were performed using Stata versions 12.1 (Study I) and 14.0 (Studies II and III), StataCorp LP. Statistical significance was assessed using two-tailed 0.05-level tests.

4.2 HAIR CORTISOL OR CORTISONE AND BRAIN MORPHOLOGY (STUDY IV)

4.2.1 Data sources

The Generation R Study is an ongoing population-based cohort study in Rotterdam, the Netherlands (122). It aims to investigate the environmental and genetic factors associated with growth, development and health from fetal life toward adulthood. In total, 9,778 pregnant women in Rotterdam were enrolled in the study from April 2002 until January 2006. Data collection started from the early prenatal phase and currently has been conducted in early teens. Overall response rate was 61% at baseline, and around 80% in follow-up until the age of 10 years. At the age of 6 –10 years all participating children and their parents were invited to the research center in the Erasmus MC-Sophia Children's Hospital. Data collection included questionnaires, interviews, hands-on measurements, behavioral observations, biological samples and magnetic resonance imaging (MRI) scans. Information used in this thesis included: assessment of hair cortisol and cortisone concentrations, structural brain imaging, body mass index (BMI), and cognitive and behavioral assessment of the children, as well as demographics of the parents.

4.2.2 Measurement of exposure and outcome

4.2.2.1 Hair cortisol and cortisone concentrations

Hair collection started nearly 2 years after the onset of the follow-up wave at the age of 6 years (123). Hair samples of the children were collected during a visit at the research center. Approximately 100 strands of hair were cut from the posterior vertex of the head, and stored in an envelope with the scalp end marked. The measurement of cortisol and cortisone was

conducted by the Laboratory of Neuro-endocrinology, Department of Internal Medicine, Erasmus Medical Center (124, 125). Briefly, the proximal 3 cm of the hair samples were weighed, minced, washed in isopropanol (LC-grade), and left to dry for a minimum of 2 days. After adding deuterium labeled cortisol and cortisone, the steroids were extracted using methanol (LC-grade). The extracts were then centrifuged and evaporated to dryness at 37℃ under a constant flow of N_2. After reconstitution in methanol (LC-grade), the extract was washed using solid phase extraction plate (Oasis HLB 96-well SPE plate, Waters Chromatography). The extracts were then evaporated to dryness at 50℃ and stored at 4℃. In the practical analysis, the extracts were resuspended in eluent, vortexed, and analyzed by liquid chromatography-tandem mass spectrometry (Xevo TQS, Waters Chromatography). As the cortisol and cortisone measures were highly skewed, all measures were log10 transformed before statistical analysis. Outliers were defined as concentrations (log10 transformed) falling below or above 3 times standard deviation from the mean.

4.2.2.2 Brain morphometric measures

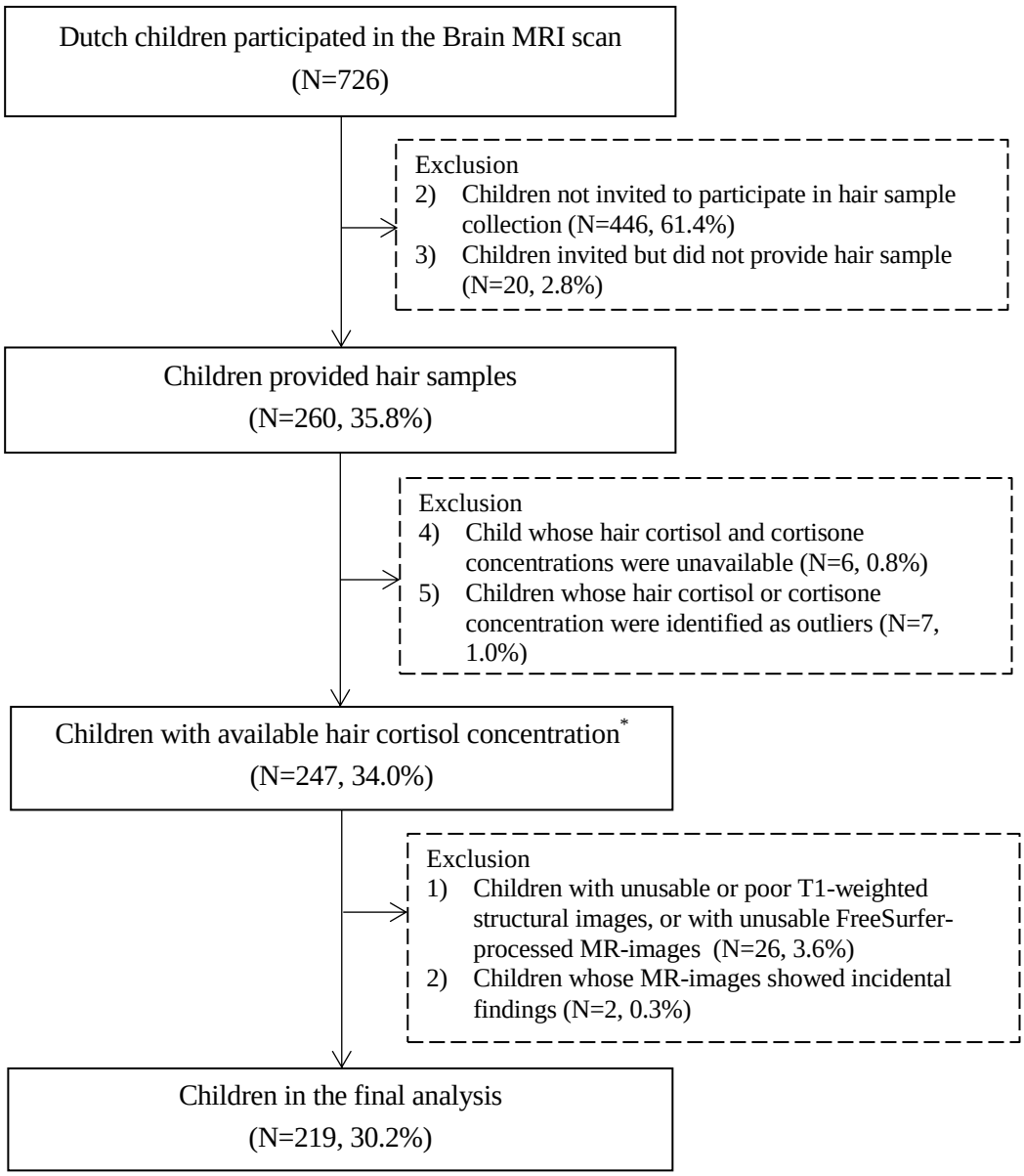
The infusion of brain MRI in the Generation R Study began in September 2009 (126). After a mock scanning session, children were scanned on a 3 Tesla scanner (General Electric Discovery MR750, Milwaukee, MI, USA) using an eight-channel head coil for signal reception. A high-resolution T_1-weighted inversion recovery fast spoiled gradient recalled sequence was obtained with the following parameters: repetition time =10.3 ms, echo time =4.2 ms, inversion time =350 ms, number of excitations =1, flip angle =16°, slice thickness=0.9mm, number of contiguous slices=186, readout bandwidth=20.8 kHz, matrix 256×256, imaging acceleration factor of 2, and an isotropic resolution of 0.9×0.9×0.9 mm^3.

Cortical reconstruction and volumetric segmentation was performed using FreeSurfer (version 5.1.0; http://surfer.nmr.mgh.harvard.edu/). FreeSurfer computes measures including volumes, cortical thickness, surface area, and gyrification in an automated approach. The technical procedures have previously been extensively described (127, 128). Cortical thickness was calculated as the shortest distance from the gray matter/white matter boundary to the gray matter/cerebrospinal fluid boundary at each vertex on the tessellated surface. Surface area was measured based on the reconstruction of cortical surface, where the cortex was segmented into units based on the patterns of gyri and sulci (129). Local gyrification index reflects the degree of cortical folding. It was measured at each vertex point on the entire brain based on the pial surface reconstruction (130).

4.2.3 Study design

Study IV was embedded in the Generation R Study. In total, 1,070 children aged 6-10 participated in the first brain MRI study (126). To achieve greater ethnic homogeneity of the participants, children of other national origins were excluded, leaving 726 Dutch children eligible for the study. The flow of inclusion and exclusion process is illustrated in Figure 5. Note that children with hair samples were less than half of the children with Brain MRI

because of the late infusion of hair sample collection. In this study, the brain MRI was conducted on average 1.6 years after the hair sample collection.



* Hair cortisone concentration was not available in 6 children

Figure 5. Flow chart of inclusion and exclusion of study participants in Study IV

4.2.4 Statistical analysis

4.2.4.1 Region of interest analysis

Linear regression was used to evaluate the associations of hair cortisol or cortisone concentration (exposure) with morphometric measures by regions of interest (outcomes). The morphometric measures included volumetrics [total brain, gray matter, white matter, cortical

gray matter, subcortical structures (subcortical gray matter, hippocampus, amygdala, caudate, putamen, pallidum and thalamus), and cortical lobes (frontal, parietal, temporal and occipital)], cortical thickness (total brain and cortical lobes), cortical surface area (total brain and cortical lobes), and local gyrification index. The models were adjusted for potential confounders, including sex, age at MRI scan, time interval between hair collection and MRI scan, Child Behavior Checklist total problems score, non-verbal IQ, BMI standard deviation score, maternal educational level, maternal age at child's birth and monthly household income. Analyses of volumetrics regarding subcortical structures and cortical lobes were performed taking into account total brain volume as a covariate. Analyses of cortical surface area for cortical lobes were performed taking into account total surface area as a covariate.

We used the Child Behavior Checklist to assess behavioral and emotional problems. A total problems score greater than 91st percentile based on a Dutch reference population was used to define a clinical behavioral problem (131). Interaction tests were performed to examine if the studied associations differed between children with and without behavioral problems.

All statistical analyses were performed using SAS version 9.4.

4.2.4.2 Vertex-wise analysis

As the *a priori*-defined regions of interest may limit the identification of the studied association elsewhere, we performed vertex-wise analyses using the FreeSurfer's Query, Design, Estimate, Contrast (QDEC) interface. It allows users to perform group averaging and inference with general linear models on cortical morphometric data computed by the FreeSurfer processing stream. Analyses were adjusted for sex (discrete factor), age at MRI scan and time interval between hair collection and MRI scan (nuisance factors). Multiple testing was corrected for by the built-in Monte Carlo simulation at a threshold of $P<0.05$, because the analysis was performed on more than 160,000 vertices (132). To assess the potential false negatives introduced by correction for multiple testing, an uncorrected statistical threshold of $P<0.001$ was also considered to approximate a significant threshold, especially for associations shown in the *a priori*-defined regions.

5 RESULTS

5.1 PARENTAL CANCER AND CHILDREN'S WELL-BEING (STUDIES I, II & III)

5.1.1 Descriptive characteristics

An overview of the study participants are shown in Table 3.

Table 3. Overview of the study participants in Studies I, II and III

Outcomes	Unexposed children	Exposed children
	No parental cancer during pregnancy	Parental cancer during pregnancy
Psychiatric disorder diagnosis		
No. of events	1,078	119
Person-years	97,392	9,923
Event rate (95% CI) [1]	11.1 (10.4−11.8)	12.0 (10.0−14.4)
Prescribed psychiatric medication		
No. of events	825	106
No. of observations	10,260	1,046
Proportion (%)	8.0	10.1
	No parental cancer after birth	Parental cancer after birth
Hospital contact for injury		
No. of events	548,488	15,377
Person-years	11,879,075	298,302
Event rate (95% CI) [1]	46.2 (46.1−46.3)	51.6 (50.7−52.4)
Psychiatric disorder diagnosis		
No. of events	81,164	8,707
Person-years	6,167,229	627,972
Event rate (95% CI) [1]	13.2 (13.1−13.3)	13.9 (13.6−14.2)
Prescribed psychiatric medication		
No. of events	89,452	9,906
No. of observations	991,938	100,166
Proportion (%)	9.0	9.9
Low intellectual performance [2]		
No. of events	93,515	4,107
No. of observations	444,866	20,383
Proportion (%)	21.0	20.2
Low stress resilience [2]		
No. of events	87,897	4,357
No. of observations	444,866	20,383
Proportion (%)	19.8	21.4
Low physical fitness [2]		
No. of events	58,877	2,799
No. of observations	444,866	20,383
Proportion (%)	13.2	13.7

[1] Number of events per 1,000 person-years

[2] Only boys

Collectively, children with parental cancer had smaller gestational age at birth, higher proportion of being delivered through caesarian section, higher proportions of birth weight less than 2,500 grams or higher than 4,000 grams, older parents at birth, and higher educational levels of parents.

5.1.2 Parental cancer and children's injury, psychiatric disorder, and impaired intellectual performance, stress resilience and physical fitness

5.1.2.1 Prenatal exposure to parental cancer

Paternal cancer during pregnancy appeared to be associated with an increased risk of psychiatric disorders, primary among the girls (clinical diagnosis of psychiatric disorder: HR: 1.31, 95% CI: 0.92–1.86; prescribed psychiatric medications: OR: 1.62, 95% CI: 1.10−2.38). Maternal cancer, however, was not associated with psychiatric disorders among children.

5.1.2.2 Postnatal exposure to parental cancer

5.1.2.2.1 Overall associations

Children with parental cancer after birth had a 7% higher risk of injury (13% higher risk of repeated injuries, HR: 1.13, 95% CI: 1.12−1.15), an 8-11% higher risk of psychiatric disorder, a 9% higher risk of having low stress resilience and a 12% higher risk of having low physical fitness, than children without such experience (Table 4). No evidence was observed for an overall association between parental cancer after birth and low intellectual performance.

Table 4. Overall associations in Studies I, II and III

Outcomes	HR/OR/RRR (95% CI)
Hospital contact for injury	1.07 (1.05−1.09)
Psychiatric disorder	
Psychiatric disorder diagnosis	1.08 (1.05−1.10)
Prescribed psychiatric medication	1.11 (1.09−1.14)
Low intellectual performance [1]	1.02 (0.97−1.08)
Low stress resilience [1]	1.09 (1.04−1.15)
Low physical fitness [1]	1.12 (1.05−1.19)

[1] Only boys

5.1.2.2.2 Sex difference

Parental cancer after birth was more strongly associated with a higher risk of injury in boys than girls, but less strongly associated with a higher risk of psychiatric disorder among boys than girls (Table 5).

Table 5. Sex difference of the studied associations in Studies I and II

Outcomes	Boys	Girls	*P* for interaction
	HR/OR (95% CI)	HR/OR (95% CI)	
Hospital contact for injury	1.11 (1.08–1.13)	1.02 (0.99–1.05)	< 0.001
Psychiatric disorder			
Psychiatric disorder diagnosis	1.06 (1.03–1.10)	1.09 (1.06–1.13)	0.09
Prescribed psychiatric medication	1.08 (1.04–1.12)	1.14 (1.10–1.17)	0.046

5.1.2.2.3 Age difference

Child's age at follow-up appeared not to modify the overall associations between parental cancer after birth and injury or psychiatric disorder diagnosis (Table 6). The difference between exposed and unexposed children however applied only significantly to children at the age of 6-11 years (injury) and at the age of 12 years and above (injury and psychiatric disorder diagnosis).

Table 6. Age difference of the studied associations in Studies I and II [HR (95% CI)]

Outcomes	≤2 years	3-5 years	6-11 years	12-14 years	≥15 years
Hospital contact for injury [1]	1.21 (0.99−1.47)	1.07 (0.97−1.18)	1.08 (1.05−1.12)	1.08 (1.04−1.11)	1.06 (1.03−1.09)
Psychiatric disorder diagnosis [2]	1.97 (0.83−4.71)	1.04 (0.78−1.38)	0.99 (0.90−1.07)	1.04 (0.96−1.11)	1.09 (1.06−1.12)

[1] *P* for interaction: 0.60

[2] *P* for interaction: 0.10

5.1.2.2.4 Difference by sex of the parent with cancer

Sex of the parent with cancer did not modify the associations of parental cancer with injury, psychiatric disorder, low intellectual performance, low stress resilience and low physical fitness (Table 7).

Table 7. Difference of the studied associations according to sex of the parent with cancer in Studies I, II and III

Outcomes	Paternal cancer	Maternal cancer	*P* (Wald test)
	HR/OR/RRR (95% CI)	HR/OR/RRR (95% CI)	
Hospital contact for injury	1.08 (1.05−1.11)	1.06 (1.04−1.09)	0.48
Psychiatric disorder			
Psychiatric disorder diagnosis	1.11 (1.07−1.14)	1.06 (1.03−1.09)	0.06
Prescribed psychiatric medication	1.09 (1.06−1.13)	1.13 (1.09−1.16)	0.17
Low intellectual performance [1]	1.02 (0.94−1.10)	1.02 (0.96−1.09)	0.87
Low stress resilience [1]	1.08 (1.00−1.17)	1.10 (1.03−1.17)	0.79
Low physical fitness [1]	1.10 (0.99−1.21)	1.14 (1.05−1.23)	0.55

[1] Only boys

5.1.2.2.5 Difference according to time since cancer diagnosis

After the cancer diagnosis of parent, children experienced the highest risk of injury during the first year, after which the risk decreased and remained the same as that among children without parental cancer from the fourth year (Table 8). On the contrary, children had a higher risk of psychiatric disorder constantly over years after the parental cancer diagnosis.

Table 8. Difference of the studied associations according to the time since cancer diagnosis in Studies I and II

Outcomes	Time since cancer diagnosis [HR (95% CI)]		
	≤ 1 year	>1 and ≤3 years	> 3 years
Hospital contact for injury [1]	1.27 (1.22−1.33)	1.10 (1.07−1.14)	1.01 (0.99−1.03)
Psychiatric disorder diagnosis [2]	1.05 (0.98−1.13)	1.08 (1.03−1.14)	1.08 (1.05−1.11)

[1] *P* (Wald test): < 0.001

[2] *P* (Wald test): 0.74

5.1.2.2.6 Difference according to expected 5-year survival for cancer

Positive dose-response trends were observed: a poorer expected survival was indicated for the cancer, a higher risk of psychiatric disorder, low intellectual performance, low stress resilience and low physical fitness the affected children had (Table 9). Such pattern was not shown regarding injury.

Table 9. Difference of the studied associations according to the expected 5-year survival for cancer in Studies I, II and III

Outcomes	Expected 5-year survival for cancer [HR/OR/RRR (95% CI)]		
	Poor	Moderate	Good
Hospital contact for injury	1.02 (0.95−1.10)	1.08 (1.06−1.11)	1.06 (1.04−1.09)
Psychiatric disorder			
Psychiatric disorder diagnosis	1.20 (1.11−1.30)	1.10 (1.07−1.14)	1.03 (1.00−1.07)
Prescribed psychiatric medication	1.23 (1.14−1.33)	1.11 (1.07−1.15)	1.10 (1.06−1.14)
Low intellectual performance [1]	1.20 (1.00−1.43)	1.09 (1.01−1.18)	0.93 (0.87−1.01)
Low stress resilience [1]	1.59 (1.31−1.94)	1.09 (1.01−1.18)	1.03 (0.96−1.11)
Low physical fitness [1]	1.45 (1.14−1.85)	1.19 (1.09−1.31)	1.02 (0.94−1.12)

All *P* for trend < 0.05

[1] Only boys

5.1.2.2.7 Difference by survival status of the parent with cancer

Compared to children without parental cancer, children who experienced the death of the parent with cancer were at an even higher risk of psychiatric disorder, low stress resilience and low physical fitness than those whose parents with cancer were still alive (Table 10). An opposite pattern was observed with regard to injury.

Table 10. Difference of the studied associations according to the survival status of the parent with cancer in Studies I, II and III

Outcomes	Death of the parent with cancer [HR/OR/RRR (95% CI)]		*P* (Wald test)
	No	Yes	
Hospital contact for injury	1.09 (1.07−1.11)	0.97 (0.93−1.01)	<0.001
Psychiatric disorder			
Psychiatric disorder diagnosis	1.04 (1.01−1.07)	1.23 (1.18−1.29)	<0.001
Prescribed psychiatric medication	1.04 (1.02−1.07)	1.32 (1.27−1.38)	<0.001
Low intellectual performance [1]	0.99 (0.94−1.05)	1.11 (1.01−1.24)	0.06
Low stress resilience [1]	1.03 (0.98−1.10)	1.29 (1.16−1.43)	<0.001
Low physical fitness [1]	1.05 (0.98−1.13)	1.40 (1.23−1.59)	<0.001

[1] Only boys

5.1.2.2.8 Impact of parental psychiatric disease

A history of psychiatric disease in the parent before cancer diagnosis did not modify the association between parental cancer and psychiatric disorder diagnosis (without history: HR: 1.08, 95%CI: 1.06−1.11, with history: HR: 1.03, 95%CI: 0.97−1.08, *P* for interaction: 0.07). However, the psychiatric disease comorbid after cancer diagnosis in the parent conferred an even higher risk of psychiatric disorder diagnosis as well as injury, compared with children whose parents with cancer without such experience (Table 11).

Table 11. Difference of the studied associations according to comorbid psychiatric disease in the parent after cancer diagnosis in Studies I and II

Outcomes	Parental psychiatric disease after cancer diagnosis [HR (95% CI)]		*P* (Wald test)
	No	Yes	
Hospital contact for injury	1.06 (1.05−1.08)	1.21 (1.12−1.31)	0.001
Psychiatric disorder diagnosis	1.04 (1.02−1.07)	1.77 (1.64−1.92)	<0.001

5.1.2.2.9 Different types of injuries

In Study I, unintentional injuries represented 96% of all injuries among the participating children (HR: 1.07, 95% CI: 1.05−1.09). Although a higher risk was also suggested for intentional self-harm, the association was not statistically significant (Figure 6). During the entire follow-up, the association between parental cancer and childhood injury did not appear to vary according to nature, body region, or mechanism of injury, or place of injury occurrence. However, during the first year after cancer diagnosis, the risk increment of transport-related injuries was likely most pronounced.

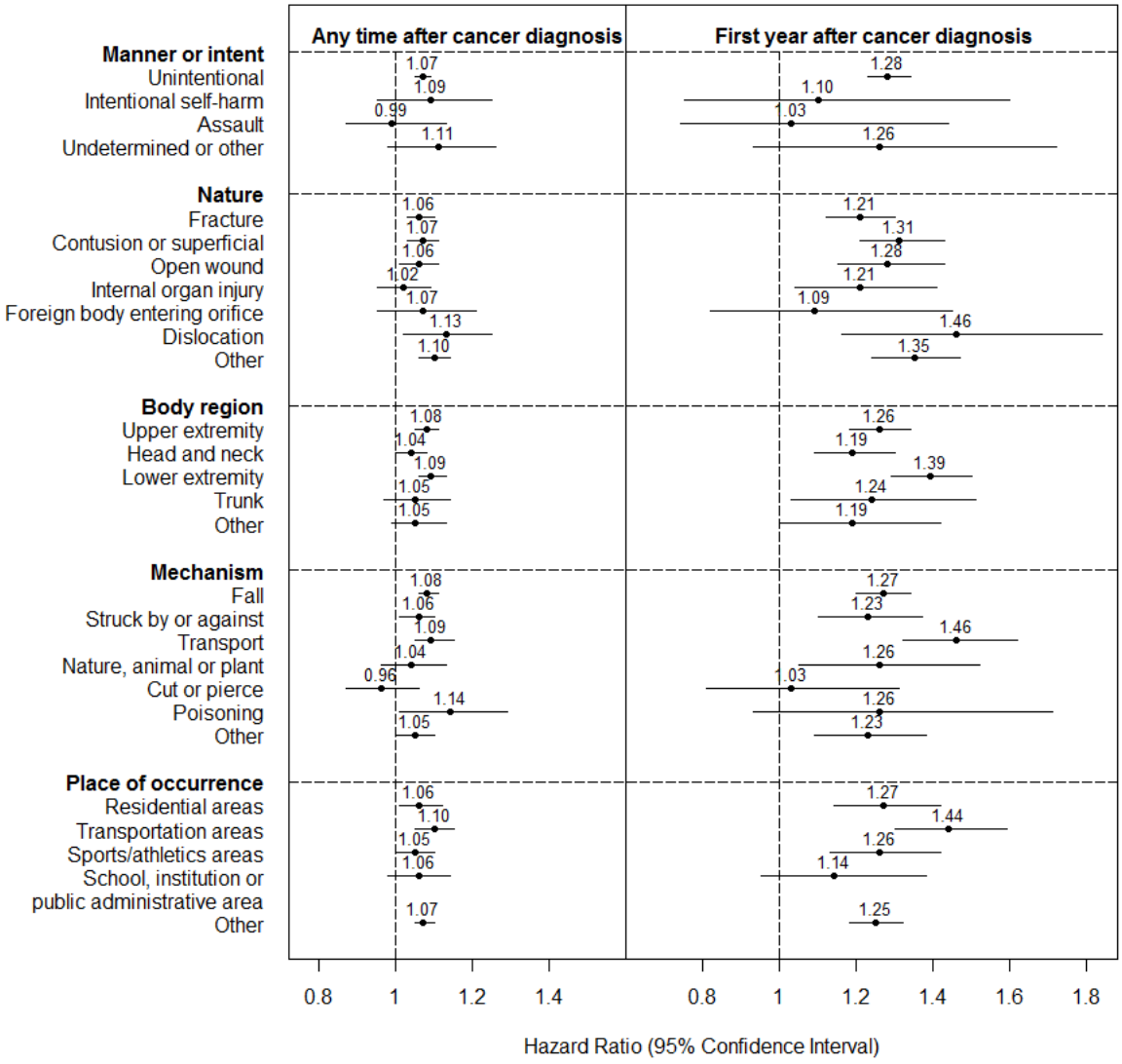


Figure 6. Hazard ratios for injury comparing children with and without parental cancer, according to different characteristics of injury (Study I; modified based on Figure 1 in paper 1)

5.1.2.2.10 Different types of psychiatric disorder

Parental cancer after birth was most strongly associated with a higher risk of stress reaction and adjustment disorders among both boys (HR: 1.24, 95%CI: 1.08–1.43) and girls (HR: 1.27, 95%CI: 1.14–1.41). Such exposure was also associated with a higher risk of affective disorders (HR: 1.10, 95%CI: 1.04−1.15) and anxiety disorders (HR: 1.06, 95%CI: 1.01−1.11), particularly in girls. No association was observed for substance use disorders, eating disorder, autism spectrum disorder or ADHD. Nevertheless, children with parental cancer had a higher risk of use of commonly prescribed psychiatric medications, including antidepressants (OR: 1.11, 95%CI: 1.08−1.14), anxiolytics (OR: 2.18, 95%CI: 2.11−2.25), and hypnotics and sedatives (OR: 1.13, 95%CI: 1.10−1.17).

5.2 HAIR CORTISOL OR CORTISONE AND BRAIN MORPHOLOGY (STUDY IV)

A total of 219 children (102 boys and 117 girls) were included in the analysis. The mean age at hair collection was 6.0 years, and the mean age at MRI scan was 7.7 years. Approximately 6.4% of the children had behavioral problems. The mean concentration (log10 transformed) of hair cortisol and cortisone was 0.13 pg/mg and 0.84 pg/mg respectively.

The regions of interest analyses showed that hair cortisol (B: 6.03, 95% CI: 1.17–10.89) and cortisone (B: 10.42, 95% CI: 2.88–17.96) concentrations were positively associated with cortical surface area in the parietal lobe. Clinical behavioral problem modified the association between hair cortisol or cortisone concentration and hippocampal volume in children (*P* for interaction <0.001): high concentrations of both hair cortisol (B= -1.54, 95% CI: -2.33 – -0.76) and hair cortisone (B= -2.17, 95% CI: -3.48 – -0.86) were associated with smaller hippocampal volume in children with behavioral problems, whereas such association was not shown in children without behavioral problems (cortisol: B: 0.10, 95% CI: -0.13 – 0.33; cortisone: B: 0.22, 95% CI: -0.12 – 0.56). No evidence was observed for an association of hair cortisol or cortisone concentration with cortical thickness or gyrification.

The vertex-wise analyses did not show any associations of hair cortisol and cortisone concentrations with brain morphometric measures after correction for multiple testing.

6 DISCUSSION

6.1 FINDINGS AND IMPLICATIONS

6.1.1 Parental cancer and children's physical health

This thesis first provides new evidence about the physical health of children impacted by parental cancer. Overall, parental cancer after birth was associated with a higher risk of injury, particularly among boys. Similarly, a higher risk of low physical fitness was observed among boys when entering adulthood. Reassuring, the increased risk of injury declined to null after three years following the cancer diagnosis; however, the impaired physical fitness persisted until early adulthood and became more pronounced after the death of the ill parent.

There are several possible explanations for these results. The higher risk of injury may primarily be attributable to lack of parental supervision caused by the immediate "crisis" of the cancer diagnosis, in addition to psychological distress experienced by the children (133, 134). The occurrence of injury raised the possibility that parents may associate their children's impaired well-being with their illness and affected parenting, so that they sought support to better protect their children. However, physical fitness was still compromised. Given that child's physical activity level was positively correlated with parent's physical activity level (135), low physical fitness could be related to the reduced daily activity of the parent with cancer and the caregiving spouse. Moreover, adverse life events have been associated with less healthy behaviors such as increased television watching, and increased smoking and alcohol use, which may also lead to decreased physical fitness (136, 137). The long-term physical health consequences of childhood experience of parental cancer deserve further careful investigation.

6.1.2 Parental cancer and children's mental health

With novel evidence from use of prescribed psychiatric medication, this thesis confirms the association between parental cancer and a higher risk of psychiatric disorder among children (30). Two recent Nordic cohort studies investigated the association between parental cancer and hospital-based psychiatric disorder diagnosis (30, 55). In accordance with the Finnish study based on a birth cohort of 59,476 children, our data consisted of a larger population (N=1,114,729) and showed that the affected girls were more likely to have a psychiatric disorder than boys. The Danish study showed no overall risk of psychiatric disorder in children exposed to parents with cancer, which may however be due to the inclusion of psychiatric disorders diagnosed only before 15 years of age (55).

Children affected by parental cancer were at a higher risk of stress reaction and adjustment disorders. Additionally, our findings corroborate the hypothesis that parental cancer as an early adversity contributed to the vulnerability to maladaptive response to future stress (138). The alterations in the stress mechanisms may also lead to a higher susceptibility to psychiatric disorders in individuals that have experienced childhood adversities (139).

6.1.3 Psychological stress, brain and cognitive ability

Stress can cause detrimental effect on the brain regions that subserve the high order cognitive abilities, such as hippocampus and prefrontal cortex (140, 141). In this thesis, no evidence was found connecting parental cancer diagnosis to impaired intellectual performance. However, a poor prognosis and the eventual loss of the parent of cancer entailed an increased risk of low intellectual performance. This result substantiates that brain regions responsible for high order cognitive abilities and feature long phases of postnatal development are more susceptible to severer stressors (142). Hippocampus is the central processing region for learning and memory (140). Hippocampus also regulates the HPA axis activity as it contains a high concentration of glucocorticoid receptors (143). A long-term consequence of childhood adversity, such as parental cancer, was higher susceptibility to psychiatric problems (75). Such chronic stress or prolonged glucocorticoids exposure can impair the hippocampus by producing dendritic retraction, which corresponds to hippocampus-dependent cognitive abilities (144, 145). Elevations in glucocorticoids associated with psychological stress may also affect emotion processing in regulating behaviors by actions on different brain regions, particularly hippocampus (146). The interrelationship and the underlying mechanism of early adversity, HPA axis activity, brain development, and cognitive and mental health is an important issue for future research, and longitudinal studies with comprehensive measurements need to be undertaken.

6.1.4 Sex and age difference

Being aware of what to expect after a parental cancer diagnosis among boys and girls with different ages allow parents and physicians to be alert to problems and respond in helpful ways. On one hand, we found that the exposed girls had a higher risk of psychiatric disorders than the exposed boys, which corroborates the sex difference in children's psychological adjustment to parental cancer (44, 147-149). On the other hand, boys were more likely to experience injuries than girls after parental cancer. The sex difference may be due to the differential ways that boys and girls respond to psychological stress (134). Girls tend to be more socially and emotionally mature than boys of the same age (149). Girls also communicate more openly about their problems and concerns with the parents (60), whereas boys engage in more risk-taking and contact sport resulting in the occurrence of injuries (150).

The previous literature on the age difference in health outcomes affected by parental cancer produced mixed results (58, 149, 151). We found no overall age differences in risk of injuries and psychiatric disorders. However, the association was more pronounced in adolescents. Young children depend more on day-to-day care of the parents, but they may not be mentally mature to understand the significance and consequence of parental cancer (29, 152). Adolescents are in the phase of developing independence, which may be interrupted by the increased burden from taking over responsibility from the ill parents (153). Nevertheless, the sex and age difference may just reflect the prominent difference regarding child's developmental trajectory shown in normal population (154).

6.1.5 Characteristics of parent and cancer

Previous studies reported mixed findings regarding the impact by sex of the parent with cancer (61, 149, 153, 155, 156). Some findings indicated greater impact by maternal cancer as mother was the primary caregiver (51, 60). Other evidence was found that ill fathers might experience more psychological stress due to the household income insecurity caused by loss of employment status during the course of disease (157). In this thesis, the associations between parental cancer and various health outcomes among children were similar for both paternal and maternal cancer. Swedish fathers have greater involvement in child-rearing thanks to the Swedish parental leave policies, and therefore a smaller gender difference in household work and parenting allows children to form equally strong attachment to both mother and father (158).

The time shortly after cancer diagnosis and the time of death is the most critical moment during the disease process. In this thesis, the first year after cancer diagnosis showed a strong association with childhood injury, and the impact of parental cancer decreased with the lapse of time. In contrast, the risk of psychiatric disorder remained constant with time since cancer diagnosis of parent and became even more pronounced after the parent deceased. Several explanations are plausible. The first year after diagnosis may be so stressful for the parents that parenting was compromised when parents were distracted by tackling the diagnosis and subsequent treatments (153). We hypothesized that parenting, compared to psychological stress experienced by children, largely accounted for the higher risk of injury in the first year. This was also supported by the fact that no difference was detected in the risk increment for unintentional and intentional injuries. Such time pattern was not shown for psychiatric disorder because of the possibilities that the consequences of a severe stressful life event do not become noticeable until later (153) and that the development of psychiatric disease is time-dependent. Nonetheless, the actual loss of parent through death entailed exceptionally adverse effect on children's mental health (159).

A poor prognosis does not necessarily relate to the adjustment status of the parent with cancer (42). Our findings, however, indicated that a poorer prognosis was associated with a higher risk of psychiatric disorder and low stress resilience among children. Having a perception of greater seriousness and stressfulness, children may have least ability to tolerate the stress and frustrations associated with the parent's illness, and they may also use more maladaptive coping strategies (160). We lacked information about the stage and treatment of cancer, which might also be associated with children's adjustment and well-being (61, 149, 155, 161-163).

Apart from the clinical conditions, the adjustment status of the parents to cancer contributed remarkably to the well-being of children (58, 151, 162, 164, 165). The occurrence of both injury and psychiatric disorder were elevated when the parent was diagnosed with psychiatric disorder after the diagnosis of cancer (30). The accumulated problems in parents may aggravate both difficulties in parenting and psychological strain for the children.

Parents should be helped to balance the attention between the illness as well as treatment and parenting of the children, especially when the cancer disease is severe, fatal and comorbid with psychiatric diseases. Support for injury prevention should also be targeted during the first few years after cancer diagnosis and particularly in transportation areas.

6.1.6 Prenatal exposure to parental cancer

When a mother has cancer during pregnancy, fetus might be exposed to not only the biology of malignancy and the toxic effects of cancer treatment (166), but also the maternal distress, as the cancer brings about severe psychological stress. This thesis provides new evidence for the long-term psychiatric outcomes associated with prenatal exposure to cancer of both parents. Only paternal but not maternal cancer during pregnancy was associated with a higher risk of psychiatric disorder. This might be due to the fact that a paternal cancer leads to a more dramatic decline in household income and socio-economic status, which are factors associated with mental health, and that the observed association might rather be due to postnatal changes (7, 167). Nevertheless, whether such difference was due to chance finding needs to be verified in future studies.

6.1.7 Significance

According to the Swedish Health Care Act [Swedish: Hälso- och sjukvårdslag (1982:763)] (168), when children live with a parent with a serious illness, their need for support and care must be taken into account for health care services. In Sweden, cancer is the second leading cause of death, and the number of cancer patients that potentially have minor children has doubled during the last forty years (31). However, no research has provided a comprehensive evaluation of the health of these children. This thesis provides important information about children's physical and mental well-being affected by parental cancer diagnosis using data from Swedish national registers. This information stands as strong evidence for concrete actions to be taken to support the children and their families. In addition, this thesis explores the potential mechanism determining the health consequences of childhood psychological stress, combining evidence from solid clinical diagnoses, biological samples and brain imaging.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Validity

6.2.1.1 Selection bias

Selection bias originates from the process of selection of study subjects or from factors that affect the study participation (169). Use of Swedish national register data has allowed us to eliminate, to a large extent, the potential selection bias, because the national coverages of the registers are generally high.

In Studies I, II and III, a potential source of selection bias was left truncation (e.g., exclusion of children who emigrated before the start of follow-up) or right censoring (e.g., exclusion of boys who emigrated before conscription). As no evidence has shown that emigration was related to either exposure or outcomes, we believed those that were excluded were a random sample of all study subjects and were therefore noninformative.

In Study IV, non-response and loss to follow-up may lead to selection bias if the association between hair cortisol or cortisone concentration and brain morphometric measures differed between children who did not participate or lost to follow-up and children included in this study. In the follow-up wave at the age of 6 years of the Generation R Study, the brain imaging component and hair sample collection were conducted only in sub-populations (122). Therefore, selection bias has also likely occurred due to the inclusion restriction in children with complete information on both exposures and outcomes.

6.2.1.2 Information bias

Information bias, also referred to as misclassification, arises when placing someone in an incorrect category due to errors during information collection (169).

In Studies I, II and III, misclassification of exposure was less likely to occur because the diagnosis of cancer in parents were identified from the Swedish Cancer Register, which has almost completely covered all incident cancer cases in the country. Potential misclassification of outcomes should be noted as only around 80% of clinical diagnoses made by specialists were reported to the Patient Register (170). Moreover, diagnostic, translation and coding error have been detected in a small proportion of records in the Patient Register (101). However, the underreporting and diagnostic coding errors were largely administrative and not likely to be related to the study hypotheses of parental cancer. Such misclassification should therefore be non-differential. Arguably, medical care seeking for child's disease might be facilitated by the established contact with health care providers among parents with cancer. Nonetheless, the opposite could also be put forward that it is less likely to seek medical care for mild conditions in children when parents are tackling their severe illnesses.

6.2.1.3 Confounding

Confounding is an important issue in observational epidemiological studies. It implies that the effect of the exposure on the outcome is mixed by the effect of another factor, i.e., confounder (169).

In the analyses of Studies I, II and III, we took into account of a couple of variables including age or birth year, sex, birth characteristics, number of siblings of the children as well as age, educational level and socio-economic status of the parents. However, residual confounding due to unmeasured confounders cannot be excluded. For instance, information on cohabitation of the parents may be of great importance. Cancer risk might differ among people with different marital status, and the risk of different health outcomes in children might differ by parental marital status. Parental separation or divorce may further impose a

negative impact on children's well-being because of altered family routines, resulting from the departure of one parent from daily life or a joint custody arrangement with both parents (75). Further work is required to assess the potential effect of residential status of the family members and the cohabitation of the parents on the studied associations. Previous studies have shown, although not conclusive, common genetic determinants of some cancers and autism (171). If such genetic connection is also present for other psychiatric disorders, our results in Study II may have been confounded by shared genetic factors.

6.2.2 Precision

The aim of epidemiological studies is to obtain a valid and precise estimate of the association between exposure and outcome (169). An estimate with small random error may be described as precise. One source of random error arises from the within-person fluctuation in the technical measurement, such as variation in cortisol assessment and brain imaging in Study IV. We addressed that by a series of procedures such as excluding outliers of cortisol and cortisone and images of poor quality. Another type of random error is sampling error during the process of selecting study subjects. In this thesis, the possibility of sampling error has largely been ruled out by using population-based design. Precision of estimation is reduced when the sample size is small. For example, the small number of children exposed to prenatal maternal cancer might have hindered us from concluding based on the wide 95% confidence intervals.

6.3 ETHICAL CONSIDERATIONS

The studies included in this thesis cover data collected from two different data sources – Swedish national registers and the Generation R Study in Rotterdam, the Netherlands, which involved different ethical considerations for the conduct of research.

According to the current Swedish regulation, informed consent is not required for use of data from the national registers with research purposes. However, the research aims and protocols must be reviewed by an ethical review board (172). Only when an ethical approval is granted can one initiate the project. To prevent one from tracking the identity of participating subjects, the individual personal identity numbers of the register data is replaced by unique serial numbers before delivered to researchers. In this thesis, Studies I, II and III used the Swedish national register data and have been approved by the Central Ethical Review Board in Stockholm, Sweden.

The Generation R Study is a population-based cohort including research on identifiable human data and materials. It has been conducted in accordance with ethical principles for medical research involving human subjects stated in the Declaration of Helsinki. The Generation R Study has undertaken several strategies to protect the participants' health and rights. A letter with information about the research was sent to the potential participants with a general leaflet on brain imaging. Research aim, importance of participation, and the

non-invasiveness and safety of MRI exams were clearly stated. After a week, the parents were contacted via phone by an employee of the Generation R Study for availability for their children. If they wanted to participate, an appointment confirmation with further information about the study will be sent as well as the informed consent. Although no evidence has shown that the brain imaging is leading to anxiety problems, some children may feel scared. A mock session was performed to help ease their fears. But if one remained anxious, the examination was stopped. Moreover, according to the principles of the code of conduct for resistance in minors participating in medical scientific research stated by the Dutch Society of Pediatrics, the children can withdraw from the study anytime. All data collected from the participants were anonymously processed. Study IV has been approved by the Medical Ethics Committee of the Erasmus University Medical Center, Rotterdam. Parents of all participating children provided written informed consent.

7 CONCLUSIONS

- Parental cancer after birth is associated with a higher risk of childhood injury, particularly during the first year after cancer diagnosis and when the parent has a comorbid psychiatric illness after cancer diagnosis. The risk increment declines during the second and third years after cancer diagnosis and becomes null afterwards.
- Paternal cancer during pregnancy appears to be associated with a higher risk of psychiatric disorder, particularly among girls. Such association is not observed for maternal cancer during pregnancy.
- Parental cancer after birth is associated with a higher risk of clinical diagnoses of psychiatric disorders and use of prescribed psychiatric medications. Parental cancer after birth is also associated with a higher risk of low stress resilience and low physical fitness in young adult men. These associations are most pronounced for parental cancer with poor expected survival and for parental death after cancer diagnosis.
- Boys with a parent that has poor expected survival for cancer or deceases after the diagnosis of cancer have a higher risk of low intellectual performance than boys without such experience.
- Hair cortisol and cortisone concentrations are positively associated with cortical surface area in the parietal lobe in young children. Hair cortisol and cortisone concentrations are inversely associated with hippocampal volume among young children with behavioral problems. No association remains significant however after correction for multiple testing.

8 FUTURE PERSPECTIVES

8.1 FOR RESEARCH ON CHILDREN WITH PARENTAL CANCER

Although some children with parental cancer have mental and physical complaints, the majority stay healthy. This raises an interesting question about what have made them react differently, i.e., healthy or even healthier as compared to being less healthy. Previous studies have suggested that children may experience positive changes after the occurrence of parental cancer, such as increased self-respect, personal growth and appreciation for life (153, 173). Additional studies will be needed to identify the determinants for such "Posttraumatic Growth" in children with parental cancer in a wider context (174), which may further guide the child-focused psychosocial intervention in the family.

8.2 FOR RESEARCH ON PSYCHOLOGICAL STRESS AND CHILDREN'S HEALTH

A cancer diagnosis in a parent is a severe stressful life event. We should note that other life threatening diseases in parents may also yield remarkable psychological strain in the children. This is an important issue for future research that identifies the high-risk child population who has significant physical and mental morbidity and who most benefits from medical and social support.

We still have a long way to go before we can completely define the mechanisms underlying psychological stress, health and development of children. To get closer to the truth, we can initiate large-scale studies based on register data, where longitudinally collected information on stressful life events, life-style factors, biological samples and neuroimaging should be warranted.

9 ACKNOWLEDGEMENTS

I could not have written this book without drawing upon the efforts and hard work for making the Swedish national registers such unique data sources for epidemiological studies. I thank the Swedish National Board of Health and Welfare, Statistics Sweden, and many scientists that have made it possible to use register data for large scale population-based research.

The Generation R Study is conducted by the Erasmus University Medical Centre in close collaboration with Erasmus University Rotterdam and the Municipal Health Service Rotterdam. I would like to gratefully acknowledge the contribution of all participating children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam, the Netherlands.

Innumerable people have left their mark on this long journey. A few of them deserve special thanks for the support, encouragement and love they gave me throughout the journey. I wish to take this opportunity to express my heartfelt gratitude to:

Fang Fang, my main supervisor, who has warmly taken me as a doctoral student, believed in me and guided me through these years. You are the most wise, energetic and loving person I've ever met. I envy your talent, vision and passion for research, and I'm deeply impressed and inspired by your courage and strong mind when facing difficulties. Thank you so much for always being there to meet, to discuss, and to help whenever needed, and for giving me both advice and freedom to develop to be an independent researcher.

Unnur Valdimarsdóttir, my co-supervisor – for the brainstorming and insights that improved the flow of the projects and manuscripts greatly. I will never stop missing the bright smiles and the warm, strong and big hugs you gave me.

Katja Fall, my co-supervisor – for the invaluable discussions and sharing of knowledge and research experience. You are always so thoughtful and cheery to me. Thank you for giving me the opportunity to continue working with you in the future.

Kamila Czene, my co-supervisor – for sharing her profound knowledge in cancer research. You always have extraordinarily insightful views upon the project work. I admire your confidence and strength in doing research.

Henning Tiemeier, my mentor at Erasmus MC, who kindly introduced me to the world of child psychiatry. Your doubting and believe made me grow. Under the harsh exterior I saw a warm heart hidden, as you always gave me the most sincere advice and suggestion for both work and life. Working with you was incredibly inspiring, and a superb experience.

Arvid Sjölander, a rock of biostatistics – for being the role model in teaching and research. Thank you so much for all the short and lengthy discussions, all your classes, and all your writings on papers and whiteboards.

Tonya White, my co-mentor at Erasmus MC – for giving me the opportunity to join the KNICR group, and sharing her bike that allowed me to explore the beauty of Rotterdam.

Amanda Regodón Wallin, my beautiful-hearted colleague and friend – for being my little "sister" in Sweden. I feel blessed to have a friend like you, who pursues excellence in work and peace in life. I am thankful for your help and support, and I am so proud of the work we have accomplished together. Your talent will shine in both clinical and research world.

Beatrice Kennedy, my brilliant collaborator – for bringing complementary expertise in solving problems, and providing insightful and helpful feedback to the research.

Ryan Muetzel, a rock of neuroimaging – for being generous to share his knowledge and skills, and taking the time to introduce MRI, to explain the analysis pipelines, and to provide valuable feedbacks to the research.

Eva Norén Selinus, Weimin Ye, Catarina Almqvist, Hanan El Marroun, Frank Verhulst, Gerard Noppe, Elisabeth van Rossum and Vincent Jaddoe – for providing their expertise, time and perspectives on the manuscripts. A special thanks goes to Weimin Ye, who kindly offered me an opportunity of epidemiological field work training in China.

Zhiwei Liu, my university classmate in China and office mate in Sweden who for the first time introduced KI to me – for his help and support, and most of all for his friendship. Your dedication in science has always inspired me. I look forward to a nice scientific collaboration between us.

Daniela Mariosa, Donghao Lu, Jianwei Zhu, Qing Shen, Elisa Longinetti, Solmaz Yazdani, Elin Roos, Anna Berglund, Amelie Plymoth, Ulrika Zagai, Marie Lindén, Alexander Ploner, Huan Song, Jiaqi Huang, Tracy Peters, Tingting Huang, Donal Barrett, Alessandra Grotta, Rie Habuka, Lijie Ding, Shuyang Yao, Tong Gong, Jiangrong Wang, Xu Chen, Wei He, Fei Yang, Ci Song, Zheng Chang, Bojing Liu, Qi Chen, Yunzhang Wang, and other colleagues at MEB or once at MEB – for the support, scientific interactions and fun activities we had together, and for making MEB a paradise to work in. To Hai-Yun Wang, Weiyao Yin, and Jie Song, I extend tremendous appreciation for the friendship you share together.

Laura Blanken, Alexander Neumann, Elize Verhoeff, Nina van Mil, Ivonne Derks, Desana Kocevska, Rosa Mulder, Jelena Milic, Unal Mutlu, Sonja Swanson and other colleagues at Erasmus MC – for so kindly welcoming me to the 28th floor, and sharing their expertise and knowledge during my visit; Azusa Hashimoto, Alexandra Cristobal Huerta, Qi Wang and Andrea Cortés– for every moment – laughing, eating, dancing, watching soccer games, running, traveling – that I've shared together on the land of windmills and tulips.

My dearest grandma, dad, mom and Shingho – for their faith in me and endless love throughout my life; Yiqiang – for being such a fun-filled and dedicated companion and soulmate in my life. I love you all.

10 REFERENCES

1. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. JAMA. 2007;298(14):1685-7.

2. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology. 2001;10(1):19-28.

3. Derogatis LR, Morrow GR, Fetting J, Penman D, Piasetsky S, Schmale AM, et al. The Prevalence of Psychiatric-Disorders among Cancer-Patients. JAMA 1983;249(6):751-7.

4. Fang F, Fall K, Mittleman MA, Sparen P, Ye W, Adami HO, et al. Suicide and cardiovascular death after a cancer diagnosis. N Engl J Med. 2012;366(14):1310-8.

5. Rhee YS, Yun YH, Park S, Shin DO, Lee KM, Yoo HJ, et al. Depression in Family Caregivers of Cancer Patients: The Feeling of Burden As a Predictor of Depression. J Clin Oncol. 2008;26(36):5890-5.

6. Northouse LL. The impact of breast cancer on patients and husbands. Cancer Nurs. 1989;12(5):276-84.

7. Osborn T. The psychosocial impact of parental cancer on children and adolescents: a systematic review. Psychooncology. 2007;16(2):101-26.

8. Visser A, Huizinga GA, van der Graaf WT, Hoekstra HJ, Hoekstra-Weebers JE. The impact of parental cancer on children and the family: a review of the literature. Cancer Treat Rev. 2004;30(8):683-94.

9. Hilton BA, Elfert H. Children's experiences with mothers' early breast cancer. Cancer Pract. 1996;4(2):96-104.

10. Hymovich DP. Child-rearing concerns of parents with cancer. Oncol Nurs Forum. 1993;20(9):1355-60.

11. Christ GH, Siegel K, Freund B, Langosch D, Hendersen S, Sperber D, et al. Impact of parental terminal cancer on latency-age children. Am J Orthopsychiatry. 1993;63(3):417-25.

12. Spira M, Kenemore E. Adolescent daughters of mothers with breast cancer: Impact and implications. Clin Soc Work J. 2000;28(2):183-95.

13. Gates MF, Lackey NR. Youngsters caring for adults with cancer. Image J Nurs Sch. 1998;30(1):11-5.

14. Bylund Grenklo T, Kreicbergs U, Hauksdottir A, Valdimarsdottir UA, Nyberg T, Steineck G, et al. Self-injury in teenagers who lost a parent to cancer: a nationwide, population-based, long-term follow-up. JAMA Pediatr. 2013;167(2):133-40.

15. Steinvall K, Johansson H, Bertero C. Balancing a changed life situation: the lived experience from next of kin to persons with inoperable lung cancer. Am J Hosp Palliat Care. 2011;28(2):82-9.

16. Andreassen S, Randers I, Naslund E, Stockeld D, Mattiasson AC. Family members' experiences, information needs and information seeking in relation to living with a patient with oesophageal cancer. Eur J Cancer Care (Engl). 2005;14(5):426-34.

17. Bylund-Grenklo T, Furst CJ, Nyberg T, Steineck G, Kreicbergs U. Unresolved grief and its consequences. A nationwide follow-up of teenage loss of a parent to cancer 6-9 years earlier. Support Care Cancer. 2016;24(7):3095-103.

18. Lanius RA, Vermetten E, Pain C. The impact of early life trauma on health and disease: The hidden epidemic. 2010. New York, NY: Cambridge University Press.

19. Amato PR, Keith B. Parental divorce and the well-being of children: a meta-analysis. Psychol Bull. 1991;110(1):26-46.

20. Paolucci EO, Genuis ML, Violato C. A meta-analysis of the published research on the effects of child sexual abuse. J Psychol. 2001;135(1):17-36.

21. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLoS Med. 2012;9(11):e1001349.

22. Cerel J, Fristad MA, Verducci J, Weller RA, Weller EB. Childhood bereavement: psychopathology in the 2 years postparental death. J Am Acad Child Adolesc Psychiatry. 2006;45(6):681-90.

23. Schiff M, Pat-Horenczyk R, Benbenishty R, Brom D, Baum N, Astor RA. High school students' posttraumatic symptoms, substance abuse and involvement in violence in the aftermath of war. Soc Sci Med. 2012;75(7):1321-8.

24. Schiavone S, Colaianna M, Curtis L. Impact of early life stress on the pathogenesis of mental disorders: relation to brain oxidative stress. Curr Pharm Des. 2015;21(11):1404-12.

25. Morris JN, Martini A, Preen D. The well-being of children impacted by a parent with cancer: an integrative review. Support Care Cancer. 2016;24(7):3235-51.

26. Huizink AC, de Medina PGR, Mulder EJH, Visser GHA, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. J Child Psychol Psyc. 2003;44(6):810-8.

27. Graignic-Philippe R, Dayan J, Chokron S, Jacquet AY, Tordjman S. Effects of prenatal stress on fetal and child development: a critical literature review. Neurosci Biobehav Rev. 2014;43:137-62.

28. Weaver KE, Rowland JH, Alfano CM, McNeel TS. Parental Cancer and the Family A Population-Based Estimate of the Number of US Cancer Survivors Residing With Their Minor Children. Cancer. 2010;116(18):4395-401.

29. Syse A, Aas GB, Loge JH. Children and young adults with parents with cancer: a population-based study. Clin Epidemiol. 2012;4:41-52.

30. Niemela M, Paananen R, Hakko H, Merikukka M, Gissler M, Rasanen S. The prevalence of children affected by parental cancer and their use of specialized psychiatric services: The 1987 Finnish Birth Cohort study. Int J Cancer. 2012;131(9):2117-25.

31. Statistikdatabas för cancer (In Swedish) (http://www.socialstyrelsen.se/statistik/statistikdatabas/cancer). [Accessed March 19, 2017].

32. American Cancer Society. Cancer facts and figures 2012. (http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf) 2012. [Accessed March 19, 2017].

33. Nilsson ME, Maciejewski PK, Zhang B, Wright AA, Trice ED, Muriel AC, et al. Mental health, treatment preferences, advance care planning, location, and quality of death in advanced cancer patients with dependent children. Cancer. 2009;115(2):399-409.

34. Sjovall K, Attner B, Lithman T, Noreen D, Gunnars B, Thome B, et al. Influence on the health of the partner affected by tumor disease in the wife or husband based on a population-based register study of cancer in Sweden. J Clin Oncol. 2009;27(28):4781-6.

35. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-4.

36. Anders CK, Hsu DS, Broadwater G, Acharya CR, Foekens JA, Zhang Y, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. J Clin Oncol. 2008;26(20):3324-30.

37. Salinas CA, Tsodikov A, Ishak-Howard M, Cooney KA. Prostate cancer in young men: an important clinical entity. Nat Rev Urol. 2014;11(6):317-23.

38. The National Board of Health and Welfare, The Swedish Cancer Society. Cancer i siffror 2009 (Cancer in numbers 2009). 2009. Stockholm, Sweden.

39. Lu DH, Andersson TML, Fall K, Hultman CM, Czene K, Valdimarsdottir U, et al. Clinical Diagnosis of Mental Disorders Immediately Before and After Cancer Diagnosis A Nationwide Matched Cohort Study in Sweden. JAMA Oncol. 2016;2(9):1188-96.

40. Miovic M, Block S. Psychiatric disorders in advanced cancer. Cancer. 2007;110(8):1665-76.

41. Carlson LE, Angen M, Cullum J, Goodey E, Koopmans J, Lamont L, et al. High levels of untreated distress and fatigue in cancer patients. Br J Cancer. 2004;90(12):2297-304.

42. Mehnert A, Brahler E, Faller H, Harter M, Keller M, Schulz H, et al. Four-week prevalence of mental disorders in patients with cancer across major tumor entities. J Clin Oncol. 2014;32(31):3540-6.

43. Hurny C, Bernhard J, Coates AS, Castiglione-Gertsch M, Peterson HF, Gelber RD, et al. Impact of adjuvant therapy on quality of life in women with node-positive operable breast cancer. International Breast Cancer Study Group. Lancet. 1996;347(9011):1279-84.

44. Edwards L, Watson M, St James-Roberts I, Ashley S, Tilney C, Brougham B, et al. Adolescent's stress responses and psychological functioning when a parent has early breast cancer. Psychooncology. 2008;17(10):1039-47.

45. Archer J, Hutchison I, Korszun A. Mood and malignancy: head and neck cancer and depression. J Oral Pathol Med. 2008;37(5):255-70.

46. Van Calsteren K, Heyns L, De Smet F, Van Eycken L, Gziri MM, Van Gemert W, et al. Cancer During Pregnancy: An Analysis of 215 Patients Emphasizing the Obstetrical and the Neonatal Outcomes. J Clin Oncol. 2010;28(4):683-9.

47. Verkooijen HM, Ang JX, Liu J, Czene K, Salim A, Hartman M. Mortality among offspring of women diagnosed with cancer: a population-based cohort study. Int J Cancer. 2013;132(10):2432-8.

48. Amant F, Vandenbroucke T, Verheecke M, Fumagalli M, Halaska MJ, Boere I, et al. Pediatric Outcome after Maternal Cancer Diagnosed during Pregnancy. N Engl J Med. 2015;373(19):1824-34.

49. Stahl O, Boyd HA, Giwercman A, Lindholm M, Jensen A, Kjaer SK, et al. Risk of Birth Abnormalities in the Offspring of Men With a History of Cancer: A Cohort Study Using Danish and Swedish National Registries. J Natl Cancer I. 2011;103(5):398-406.

50. Rosenfeld A, Caplan G, Yaroslavsky A, Jacobowitz J, Yuval Y, Lebow H. Adaptation of children of parents suffering from cancer: A preliminary study of a new field for primary prevention research. J Prim Prev. 1983;3(4):244-50.

51. Welch AS, Wadsworth ME, Compas BE. Adjustment of children and adolescents to parental cancer. Parents' and children's perspectives. Cancer. 1996;77(7):1409-18.

52. Gazendam-Donofrio SM, Hoekstra HJ, van der Graaf WT, van de Wiel HB, Visser A, Huizinga GA, et al. Adolescents' emotional reactions to parental cancer: effect on emotional and behavioral problems. J Pediatr Psychol. 2011;36(3):346-59.

53. Moller B, Barkmann C, Krattenmacher T, Kuhne F, Bergelt C, Beierlein V, et al. Children of cancer patients: prevalence and predictors of emotional and behavioral problems. Cancer. 2014;120(15):2361-70.

54. Niemela M, Paananen R, Hakko H, Merikukka M, Gissler M, Rasanen S. Mental disorder diagnoses of offspring affected by parental cancer before early adulthood: the 1987 Finnish Birth Cohort study. Psychooncology. 2016.

55. Benros ME, Laursen TM, Dalton SO, Nordentoft M, Mortensen PB. The risk of schizophrenia and child psychiatric disorders in offspring of mothers with lung cancer and other types of cancer: a Danish nationwide register study. PLoS One. 2013;8(11):e79031.

56. Helseth S, Ulfsaet N. Having a parent with cancer - Coping and quality of life of children during serious illness in the family. Cancer Nurs. 2003;26(5):355-62.

57. Huizinga GA, van der Graaf WT, Visser A, Dijkstra JS, Hoekstra-Weebers JE. Psychosocial consequences for children of a parent with cancer: a pilot study. Cancer Nurs. 2003;26(3):195-202.

58. Krattenmacher T, Kuhne F, Ernst J, Bergelt C, Romer G, Moller B. Parental cancer: factors associated with children's psychosocial adjustment--a systematic review. J Psychosom Res. 2012;72(5):344-56.

59. Lewis FM, Zahlis EH, Shands ME, Sinsheimer JA, Hammond MA. The functioning of single women with breast cancer and their school-aged children. Cancer Pract. 1996;4(1):15-24.

60. Bultmann JC, Beierlein V, Romer G, Moller B, Koch U, Bergelt C. Parental cancer: Health-related quality of life and current psychosocial support needs of cancer survivors and their children. Int J Cancer. 2014;135(11):2668-77.

61. Huizinga GA, Visser A, van der Graaf WT, Hoekstra HJ, Klip EC, Pras E, et al. Stress response symptoms in adolescent and young adult children of parents diagnosed with cancer. Eur J Cancer. 2005;41(2):288-95.

62. Kuhne F, Krattenmacher T, Bergelt C, Ernst JC, Flechtner HH, Fuhrer D, et al. Parental palliative cancer: psychosocial adjustment and health-related quality of life in adolescents participating in a German family counselling service. BMC Palliat Care. 2012;11:21.

63. Measurement of and target-setting for well-being: an initiative by the WHO Regional Office for Europe. [http://www.euro.who.int/__data/assets/pdf_file/0003/180048/E96732.pdf]. [Accessed March 19, 2017].

64. Peden M, Oyegbite K, Ozanne-Smith J, Hyder AA, Branche C, Fazlur Rahman A, et al. 2008. World report on child injury prevention. Geneva, Switzerland: World Health Organization.

65. Horwitz SM, Morgenstern H, DiPietro L, Morrison CL. Determinants of pediatric injuries. Am J Dis Child. 1988;142(6):605-11.

66. Tanskanen AO. Maternal health problems correlate with increased risk of early childhood injury in the UK. [http://wpsei.utu.fi/wp-content/uploads/2016/02/Tanskanen_mat_health.pdf] 2016. [Accessed March 19, 2017].

67. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.

68. Blair SN, Kohl HW, 3rd, Paffenbarger RS, Jr., Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA. 1989;262(17):2395-401.

69. Crump C, Sundquist J, Winkleby MA, Sieh W, Sundquist K. Physical Fitness Among Swedish Military Conscripts and Long-Term Risk for Type 2 Diabetes Mellitus: A Cohort Study. Ann Intern Med. 2016;164(9):577-84.

70. Erikssen J. Physical fitness and coronary heart disease morbidity and mortality. A prospective study in apparently healthy, middle aged men. Acta Med Scand Suppl. 1986;711:189-92.

71. Statistikdatabas för diagnoser i öppen vård (In Swedish) (http://www.socialstyrelsen.se/statistik/statistikdatabas/diagnoserioppenvard). [Accessed March 19, 2017].

72. Allgulander C, Nowak J, Rice JP. Psychopathology and treatment of 30,344 twins in Sweden. II. Heritability estimates of psychiatric diagnosis and treatment in 12,884 twin pairs. Acta Psychiatr Scand. 1991;83(1):12-5.

73. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ, Sonuga-Barke EJ. Default-mode brain dysfunction in mental disorders: a systematic review. Neurosci Biobehav Rev. 2009;33(3):279-96.

74. Caspi A, Moffitt TE. Gene-environment interactions in psychiatry: joining forces with neuroscience. Nat Rev Neurosci. 2006;7(7):583-90.

75. Kessler RC, Davis CG, Kendler KS. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. Psychol Med. 1997;27(5):1101-19.

76. Wu G, Feder A, Cohen H, Kim JJ, Calderon S, Charney DS, et al. Understanding resilience. Front Behav Neurosci. 2013;7:10.

77. Rutter M. Implications of resilience concepts for scientific understanding. Ann N Y Acad Sci. 2006;1094:1-12.

78. Jensen SK, Dickie EW, Schwartz DH, Evans CJ, Dumontheil I, Paus T, et al. Effect of Early Adversity and Childhood Internalizing Symptoms on Brain Structure in Young Men. JAMA Pediatr. 2015;169(10):938-46.

79. Teicher MH, Samson JA, Anderson CM, Ohashi K. The effects of childhood maltreatment on brain structure, function and connectivity. Nat Rev Neurosci. 2016;17(10):652-66.

80. Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, et al. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse--a preliminary report. Biol Psychiatry. 1997;41(1):23-32.

81. Vythilingam M, Heim C, Newport J, Miller AH, Anderson E, Bronen R, et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. Am J Psychiatry. 2002;159(12):2072-80.

82. Bremner JD, Vermetten E, Afzal N, Vythilingam M. Deficits in verbal declarative memory function in women with childhood sexual abuse-related posttraumatic stress disorder. J Nerv Ment Dis. 2004;192(10):643-9.

83. Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat Rev Neurosci. 2009;10(6):434-45.

84. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009;5(7):374-81.

85. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res. 2002;53(4):865-71.

86. Vanaelst B, Michels N, De Vriendt T, Huybrechts I, Vyncke K, Sioen I, et al. Cortisone in hair of elementary school girls and its relationship with childhood stress. Eur J Pediatr. 2013;172(6):843-6.

87. Wosu AC, Valdimarsdottir U, Shields AE, Williams DR, Williams MA. Correlates of cortisol in human hair: implications for epidemiologic studies on health effects of chronic stress. Ann Epidemiol. 2013;23(12):797-811 e2.

88. Sauve B, Koren G, Walsh G, Tokmakejian S, Van Uum SHM. Measurement of cortisol in human hair as a biomarker of systemic exposure. Clin Invest Med. 2007;30(5):E183-E91.

89. Pruessner JC, Dedovic K, Pruessner M, Lord C, Buss C, Collins L, et al. Stress regulation in the central nervous system: evidence from structural and functional neuroimaging studies in human populations - 2008 Curt Richter Award Winner. Psychoneuroendocrinology. 2010;35(1):179-91.

90. Bremner JD. Does stress damage the brain? Biol Psychiatry. 1999;45(7):797-805.

91. Haley DW, Weinberg J, Grunau RE. Cortisol, contingency learning, and memory in preterm and full-term infants. Psychoneuroendocrinology. 2006;31(1):108-17.

92. Carrion VG, Weems CF, Ray RD, Glaser B, Hessl D, Reiss AL. Diurnal salivary cortisol in pediatric posttraumatic stress disorder. Biol Psychiatry. 2002;51(7):575-82.

93. Saridjan NS, Henrichs J, Schenk JJ, Jaddoe VW, Hofman A, Kirschbaum C, et al. Diurnal cortisol rhythm and cognitive functioning in toddlers: the Generation R Study. Child Neuropsychol. 2014;20(2):210-29.

94. Saridjan NS, Velders FP, Jaddoe VW, Hofman A, Verhulst FC, Tiemeier H. The longitudinal association of the diurnal cortisol rhythm with internalizing and externalizing problems in pre-schoolers. The Generation R Study. Psychoneuroendocrinology. 2014;50:118-29.

95. Pagliaccio D, Luby JL, Bogdan R, Agrawal A, Gaffrey MS, Belden AC, et al. Stress-System Genes and Life Stress Predict Cortisol Levels and Amygdala and Hippocampal Volumes in Children. Neuropsychopharmacology. 2014;39(5):1245-53.

96. Carrion VG, Weems CF, Richert K, Hoffman BC, Reiss AL. Decreased prefrontal cortical volume associated with increased bedtime cortisol in traumatized youth. Biol Psychiatry. 2010;68(5):491-3.

97. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-67.

98. Ekbom A. The Swedish Multi-generation Register. Methods Mol Biol. 2011;675:215-20.

99. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol. 2009;48(1):27-33.

100. Kungl medicinalstyrelsen. Statistisk klassifikation av sjukdomar, skador och dödsorsaker (http://www.socialstyrelsen.se/klassificeringochkoder/Documents/KS57.pdf) (in Swedish). [Accessed March 19, 2017].

101. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

102. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726-35.

103. Aberg MA, Waern M, Nyberg J, Pedersen NL, Bergh Y, Aberg ND, et al. Cardiovascular fitness in males at age 18 and risk of serious depression in adulthood: Swedish prospective population-based study. Br J Psychiatry. 2012;201(5):352-9.

104. Rekryteringsmyndigheten. Historik - Rekryteringsmyndigheten (http://www.rekryteringsmyndigheten.se/om-rekryteringsmyndigheten/historik/) (in Swedish). [Accessed March 19, 2017].

105. National Board of Health and Welfare. The Swedish Medical Birth Register - A summary of content and quality. (http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/10655/2003-112-3_20031123.pdf). 2003. [Accessed March 19, 2017].

106. Statistics Sweden. The Swedish Register of Education. (http://www.scb.se/statistik/UF/UF0506/Produktbeskrivning_short_English_UF0506_20040101r.doc). 2004. [Accessed March 19, 2017].

107. Statistics Sweden. MIS 1982:4. Socioekonomisk indelning (SEI) (http://www.scb.se/statistik/_publikationer/OV9999_1982A01_BR_X11%C3%96P8204.pdf) . [Accessed March 19, 2017].

108. Talback M, Stenbeck M, Rosen M. Up-to-date long-term survival of cancer patients: an evaluation of period analysis on Swedish Cancer Registry data. Eur J Cancer. 2004;40(9):1361-72.

109. Bergen G, Chen LH, Warner M, Fingerhut LA. Injury in the United States: 2007 chartbook. Hyattsville, MD: National Center for Health Statistics. (https://www.cdc.gov/nchs/data/misc/injury2007.pdf) 2008. [Accessed March 19, 2017].

110. Statistikdatabas för läkemedel [http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel] (in Swedish) [Accessed March 19, 2017].

111. Carlstedt B. Mönstring och uttagning till plikttjänst och dess relation till provresultat och psykologbedömningar: en jämförelse mellan svenskar och invandrare (in Swedish). 2002. Försvarshögskolan, Klara AB Tryckeri, Karlstad.

112. Carlstedt B. Cognitive abilities - aspects of structure, process and measurement. 2000. Göteborg: Acta Universitatis Gothoburgensis.

113. Fowler T, Zammit S, Owen MJ, Rasmussen F. A population-based study of shared genetic variation between premorbid IQ and psychosis among male twin pairs and sibling pairs from Sweden. Arch Gen Psychiatry. 2012;69(5):460-6.

114. Falkstedt D, Sorjonen K, Hemmingsson T, Deary IJ, Melin B. Psychosocial functioning and intelligence both partly explain socioeconomic inequalities in premature death. A population-based male cohort study. PLoS One. 2013;8(12):e82031.

115. Lindqvist E, Vestman R. The Labor Market Returns to Cognitive and Noncognitive Ability: Evidence from the Swedish Enlistment. Am Econ J-Appl Econ. 2011;3(1):101-28.

116. Bergh C, Udumyan R, Fall K, Nilsagard Y, Appelros P, Montgomery S. Stress resilience in male adolescents and subsequent stroke risk: cohort study. J Neurol Neurosurg Psychiatry. 2014;85(12):1331-6.

117. Tornvall G. Assessment of physical capabilities. Acta Physiologica Scandinavica Supplementum. 1963;58:Suppl. 201.

118. Nordesjo LO. Estimation of the maximal work rate sustainable for 6 minutes using a single-level load or stepwise increasing loads. Ups J Med Sci. 1974;79(1):45-50.

119. Nordesjö L, Schéle R. Validity of an ergometer cycle test and measures of isometric muscle strength when prediction some aspects of military performance. Swedish J Defence Med. 1974;10:11-23.

120. Schoenfeld D. Partial Residuals for the Proportional Hazards Regression-Model. Biometrika. 1982;69(1):239-41.

121. Prentice R, Williams B, Peterson A. On the regression analysis of multivariate failure time data. Biometrika. 1981;68:373–9.

122. Kooijman MN, Kruithof CJ, van Duijn CM, Duijts L, Franco OH, van IJzendoorn MH, et al. The Generation R Study: design and cohort update 2017. Eur J Epidemiol. 2016;31(12):1243-64.

123. Kruithof CJ, Kooijman MN, van Duijn CM, Franco OH, de Jongste JC, Klaver CC, et al. The Generation R Study: Biobank update 2015. Eur J Epidemiol. 2014;29(12):911-27.

124. Noppe G, de Rijke YB, Dorst K, van den Akker EL, van Rossum EF. LC-MS/MS-based method for long-term steroid profiling in human scalp hair. Clin Endocrinol (Oxf). 2015;83(2):162-6.

125. Rippe RC, Noppe G, Windhorst DA, Tiemeier H, van Rossum EF, Jaddoe VW, et al. Splitting hair for cortisol? Associations of socio-economic status, ethnicity, hair color, gender and other child characteristics with hair cortisol and cortisone. Psychoneuroendocrinology. 2016;66:56-64.

126. White T, El Marroun H, Nijs I, Schmidt M, van der Lugt A, Wielopolki PA, et al. Pediatric population-based neuroimaging and the Generation R Study: the intersection of developmental neuroscience and epidemiology. Eur J Epidemiol. 2013;28(1):99-111.

127. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 1999;9(2):179-94.

128. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage. 1999;9(2):195-207.

129. Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, et al. Automatically parcellating the human cerebral cortex. Cereb Cortex. 2004;14(1):11-22.

130. Schaer M, Cuadra MB, Tamarit L, Lazeyras F, Eliez S, Thiran JP. A surface-based approach to quantify local cortical gyrification. IEEE Trans Med Imaging. 2008;27(2):161-70.

131. Tick NT, van der Ende J, Koot HM, Verhulst FC. 14-year changes in emotional and behavioral problems of very young Dutch children. J Am Acad Child Adolesc Psychiatry. 2007;46(10):1333-40.

132. Hagler DJ, Saygin AP, Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. Neuroimage. 2006;33(4):1093-103.

133. Morrongiello BA, Corbett M, McCourt M, Johnston N. Understanding unintentional injury-risk in young children I. The nature and scope of caregiver supervision of children at home. J Pediatr Psychol. 2006;31(6):529-39.

134. Asbridge M, Azagba S, Langille DB, Rasic D. Elevated depressive symptoms and adolescent injury: examining associations by injury frequency, injury type, and gender. BMC Public Health. 2014;14:190.

135. Hesketh KR, Goodfellow L, Ekelund U, McMinn AM, Godfrey KM, Inskip HM, et al. Activity levels in mothers and their preschool children. Pediatrics. 2014;133(4):e973-80.

136. Stults-Kolehmainen MA, Sinha R. The effects of stress on physical activity and exercise. Sports Med. 2014;44(1):81-121.

137. Zaqout M, Vyncke K, Moreno LA, De Miguel-Etayo P, Lauria F, Molnar D, et al. Determinant factors of physical fitness in European children. Int J Public Health. 2016;61(5):573-82.

138. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry. 2001;49(12):1023-39.

139. Espejo EP, Hammen CL, Connolly NP, Brennan PA, Najman JM, Bor W. Stress sensitization and adolescent depressive severity as a function of childhood adversity: a link to anxiety disorders. J Abnorm Child Psychol. 2007;35(2):287-99.

140. McEwen BS, Sapolsky RM. Stress and cognitive function. Curr Opin Neurobiol. 1995;5(2):205-16.

141. Arnsten AF. Stress signalling pathways that impair prefrontal cortex structure and function. Nat Rev Neurosci. 2009;10(6):410-22.

142. Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl). 2011;214(1):55-70.

143. Lupien SJ, Maheu F, Tu M, Fiocco A, Schramek TE. The effects of stress and stress hormones on human cognition: Implications for the field of brain and cognition. Brain Cogn. 2007;65(3):209-37.

144. Conrad CD. Chronic stress-induced hippocampal vulnerability: the glucocorticoid vulnerability hypothesis. Rev Neurosci. 2008;19(6):395-411.

145. Conrad CD. What is the functional significance of chronic stress-induced CA3 dendritic retraction within the hippocampus? Behav Cogn Neurosci Rev. 2006;5(1):41-60.

146. Hanson JL, Nacewicz BM, Sutterer MJ, Cayo AA, Schaefer SM, Rudolph KD, et al. Behavioral problems after early life stress: contributions of the hippocampus and amygdala. Biol Psychiatry. 2015;77(4):314-23.

147. Huizinga GA, Visser A, van der Graaf WT, Hoekstra HJ, Hoekstra-Weebers JE. The quality of communication between parents and adolescent children in the case of parental cancer. Ann Oncol. 2005;16(12):1956-61.

148. Krattenmacher T, Kuhne F, Halverscheid S, Wiegand-Grefe S, Bergelt C, Romer G, et al. A comparison of the emotional and behavioral problems of children of patients with cancer or a mental disorder and their association with parental quality of life. J Psychosom Res. 2014;76(3):213-20.

149. Visser A, Huizinga GA, Hoekstra HJ, van der Graaf WT, Klip EC, Pras E, et al. Emotional and behavioural functioning of children of a parent diagnosed with cancer: a cross-informant perspective. Psychooncology. 2005;14(9):746-58.

150. Pickett W, Molcho M, Simpson K, Janssen I, Kuntsche E, Mazur J, et al. Cross national study of injury and social determinants in adolescents. Inj Prev. 2005;11(4):213-8.

151. Thastum M, Watson M, Kienbacher C, Piha J, Steck B, Zachariae R, et al. Prevalence and Predictors of Emotional and Behavioural Functioning of Children Where a Parent Has Cancer A Multinational Study. Cancer. 2009;115(17):4030-9.

152. Bonoti F, Leondari A, Mastora A. Exploring Children's Understanding of Death: Through Drawings and the Death Concept Questionnaire. Death Stud. 2013;37(1):47-60.

153. Visser A. Children's functioning following parental cancer (doctoral thesis). 2007.

154. Bongers IL, Koot HM, van der Ende J, Verhulst FC. The normative development of child and adolescent problem behavior. J Abnorm Psychol. 2003;112(2):179-92.

155. Compas BE, Worsham NL, Eppingjordan JE, Grant KE, Mireault G, Howell DC, et al. When Mom or Dad Has Cancer - Markers of Psychological Distress in Cancer-Patients, Spouses, and Children. Health Psychol. 1994;13(6):507-15.

156. Lindqvist B, Schmitt F, Santalahti P, Romer G, Piha J. Factors associated with the mental health of adolescents when a parent has cancer. Scand J Psychol. 2007;48(4):345-51.

157. Ernst J, Gotze H, Krauel K, Romer G, Bergelt C, Flechtner HH, et al. Psychological distress in cancer patients with underage children: gender-specific differences. Psychooncology. 2013;22(4):823-8.

158. Rostila M, Saarela J, Kawachi I. Mortality in parents following the death of a child: a nationwide follow-up study from Sweden. J Epidemiol Community Health. 2012;66(10):927-33.

159. Alvariza A, Lovgren M, Bylund-Grenklo T, Hakola P, Furst CJ, Kreicbergs U. How to support teenagers who are losing a parent to cancer: Bereaved young adults' advice to healthcare professionals-A nationwide survey. Palliat Support Care. 2016:1-7.

160. Compas BE, Worsham NL, Ey S, Howell DC. When mom or dad has cancer: II. Coping, cognitive appraisals, and psychological distress in children of cancer patients. Health Psychol. 1996;15(3):167-75.

161. Gazendam-Donofrio SM, Hoekstra HJ, van der Graaf WT, van de Wiel HB, Visser A, Huizinga GA, et al. Family functioning and adolescents' emotional and behavioral problems: when a parent has cancer. Ann Oncol. 2007;18(12):1951-6.

162. Huizinga GA, Visser A, Van der Graaf WT, Hoekstra HJ, Stewart RE, Hoekstra-Weebers JE. Family-oriented multilevel study on the psychological functioning of adolescent children having a mother with cancer. Psychooncology. 2011;20(7):730-7.

163. Visser A, Huizinga GA, Hoekstra HJ, van der Graaf WT, Hoekstra-Weebers JE. Parental cancer: characteristics of parents as predictors for child functioning. Cancer. 2006;106(5):1178-87.

164. Nelson E, While D. Children's adjustment during the first year of a parent's cancer diagnosis. J Psychosoc Oncol. 2002;20(1):15-36.

165. Watson M, St James-Roberts I, Ashley S, Tilney C, Brougham B, Edwards L, et al. Factors associated with emotional and behavioural problems among school age children of breast cancer patients. Br J Cancer. 2006;94(1):43-50.

166. Pentheroudakis G, Pavlidis N. Cancer and pregnancy: poena magna, not anymore. Eur J Cancer. 2006;42(2):126-40.

167. Velez CN, Johnson J, Cohen P. A longitudinal analysis of selected risk factors for childhood psychopathology. J Am Acad Child Adolesc Psychiatry. 1989;28(6):861-4.

168. Hälso- och sjukvårdslag (1982:763)(In Swedish) (https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/halso--och-sjukvardslag-1982763_sfs-1982-763). [Accessed March 19, 2017].

169. Rothman KJ. Epidemiology: An Introduction. 2nd ed. 2012. New York: Oxford University Press.

170. National Board of Health and Welfare. Kvalitet och innehåll i patientregistret Utskrivningar från slutenvården 1964–2007 och besök i specialiserad öppenvård (exklusive primärvårdsbesök) 1997–2007 (In Swedish) (http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8306/2009-125-15_200912515_rev2.pdf) 2009. [Accessed March 19, 2017].

171. Buxbaum JD, Cai GQ, Chaste P, Nygren G, Goldsmith J, Reichert J, et al. Mutation screening of the PTEN gene in patients with autism spectrum disorders and macrocephaly. Am J Med Genet B. 2007;144b(4):484-91.

172. Ludvigsson JF, Haberg SE, Knudsen GP, Lafolie P, Zoega H, Sarkkola C, et al. Ethical aspects of registry-based research in the Nordic countries. Clin Epidemiol. 2015;7:491-508.

173. Kissil K, Nino A, Jacobs S, Davey M, Tubbs CY. "It has been a good growing experience for me": growth experiences among African American youth coping with parental cancer. Fam Syst Health. 2010;28(3):274-89.

174. Teixeira RJ, Pereira MG. Factors contributing to posttraumatic growth and its buffering effect in adult children of cancer patients undergoing treatment. J Psychosoc Oncol. 2013;31(3):235-65.